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(54) Title: COMPOSITIONS, COMBINATIONS, AND METHODS FOR TREATING CARDIOVASCULAR CONDITIONS AND OTHER ASSOCIATED CONDITIONS

(57) Abstract: This invention is directed generally to a method for treating a pathological condition (particularly a cardiovascular condition (*e.g.*, hypertension or heart failure) or a condition associated with a cardiovascular condition) using a p38-kinase inhibitor (*e.g.*, a p38-kinase-inhibiting substituted pyrazole), and specifically a combination comprising a p38-kinase inhibitor with an angiotensin-converting-enzyme inhibitor (or "ACE inhibitor") for treating a cardiovascular condition. This invention also is directed generally to combinations comprising a p38-kinase inhibitor, and specifically to combinations comprising a p38-kinase inhibitor with an angiotensin-converting-enzyme inhibitor. This invention is further directed generally to pharmaceutical compositions comprising a p38-kinase inhibitor, and more specifically to compositions comprising the above-described combinations.

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COMPOSITIONS, COMBINATIONS, AND METHODS FOR TREATING CARDIOVASCULAR CONDITIONS AND OTHER ASSOCIATED CONDITIONS

PRIORITY CLAIM TO RELATED PATENT APPLICATION

[1] This patent claims priority to U.S. Provisional Patent Application Serial No. 60/450,529 (filed February 26, 2003), which is incorporated by reference into this patent.

FIELD OF THE INVENTION

[2] This invention is directed generally to a method for treating a pathological condition (particularly a cardiovascular condition (*e.g.*, hypertension or heart failure) or a condition associated with a cardiovascular condition) using a p38-kinase inhibitor (*e.g.*, a p38-kinase-inhibiting substituted pyrazole), and specifically a combination comprising a p38-kinase inhibitor with an angiotensin-converting-enzyme inhibitor (or "ACE inhibitor"). This invention also is directed generally to combinations comprising a p38-kinase inhibitor, and specifically to combinations comprising a p38-kinase inhibitor with an angiotensin-converting-enzyme inhibitor. This invention is further directed generally to pharmaceutical compositions comprising a p38-kinase inhibitor, and more specifically to compositions comprising the above-described combinations.

BACKGROUND OF THE INVENTION

[3] Mitogen-activated protein kinases (MAPKs) are collectively a family of proline-directed serine/threonine kinases that transduce signals from the cell membrane to the cell nucleus in response to a variety of signals. These kinases activate their substrates by phosphorylation. Three major subgroups of MAPKs have been identified: extracellular signal-related kinases ("ERK"), p38 MAPKs, and c-jun-NH_2 kinases (JNK).

[4] The p38 MAPKs are present in a variety of isoforms, including p38α, p38β, and p38γ. These kinases are responsible for phosphorylating and activating transcription factors (*e.g.*, ATF2, CHOP, and MEF2C), as well as other kinases (*e.g.*, MAPKAP-2 and MAPKAP-3). The p38 isoforms are activated by, for example, endotoxins (*i.e.*, bacterial lipopolysaccharides), physical cellular stress, chemical cellular stress, cell proliferation,

cell growth, cell death, and inflammation. The products of the p38 phosphorylation, in turn, mediate the production of inflammatory cytokines, such as tumor necrosis factors ("TNF"), IL-1, and cyclooxygenase-2.

[5] It has been reported that p38α kinase can cause (or contribute to the effects of), for example, inflammation generally; arthritis; neuroinflammation; pain; fever; pulmonary disorders; cardiovascular diseases; cardiomyopathy; stroke; ischemia; reperfusion injury; renal reperfusion injury; brain edema; neurotrauma and brain trauma; neurodegenerative disorders; central nervous system disorders; liver disease and nephritis; gastrointestinal conditions; ulcerative diseases; ophthalmic diseases; ophthalmological conditions; glaucoma; acute injury to the eye tissue and ocular traumas; diabetes; diabetic nephropathy; skin-related conditions; viral and bacterial infections; myalgias due to infection; influenza; endotoxic shock; toxic shock syndrome; autoimmune disease; bone resorption diseases; multiple sclerosis; disorders of the female reproductive system; pathological (but non-malignant) conditions, such as hemaginomas, angiofibroma of the nasopharynx, and avascular necrosis of bone; benign and malignant tumors/neoplasia including cancer; leukemia; lymphoma; systemic lupus erthrematosis (SLE); angiogenesis including neoplasia; and metastasis. *See, e.g.*, PCT Patent Publication No. WO 00/31063 or U.S. Patent No. 6,525,059. *See also*, PCT Publication No. WO 98/52940. *See also*, U.S. Patent No. 6,423,713.

[6] Recently, increased cardiac p38 MAPK levels and activity have been reported to be associated with human heart failure secondary to ischaemic heart disease. *See, e.g.*, Cook S.A., et al., "Activation of c-Jun N-terminal kinases and p38-mitogen-activated protein kinases in human heart failure secondary to ischemic heart disease", *J Mol Cell Cardiol.*, 31:1429-1434 (1999). *See also, e.g.*, Adams, J.W., et al., "Enhanced Gαq signaling: a common pathway mediates cardiac hypertrophy and apoptotic heart failure", *Proc Natl Acad Sci USA.*, 95:10140-10145 (1998). *See also, e.g.*, Liao, P, et al., "The *in vivo* role of p38 MAP kinases in cardiac remodeling and restrictive cardiomyopathy", *Proc Natl Acad Sci USA.*, 98:12283-12288 (2001). *See also, e.g.*, Liao, P., et al., "p38 mitogen-activated protein kinase mediates a negative inotropic effect in cardiac myocytes", *Circ Res.*, 90, No. 2: 190-96 (2002). *See also, e.g.*, Haq, S., et al., "Differential activation of signal transduction pathways in human hearts with hypertrophy versus advanced heart failure", *Circulation*, 103:670-677 (2001). It has been reported that possible stimuli for

these increases may include, for example, neurohormones, pro-inflammatory cytokines, and wall stress. *See, e.g.*, Behr, T.M., et al., "Hypertensive end-organ damage and premature mortality are p38 mitogen-activated protein kinase-dependent in a rat model of cardiac hypertrophy and dysfunction", *Circulation*, 104:1292-1298 (2001). *See also, e.g.*, Sugden, P.H., et al., "Stress-responsive" mitogen-activated protein kinases (c-Jun N-terminal kinases and p38 mitogen-activated protein kinases) in the myocardium", *Circ Res.*, 83:345-352 (1998). It has been reported that the p38-α isoform is particularly associated with inducing cardiac hypertrophy, while the p38-β isoform is more associated with cardiomyocyte apoptosis, which occurs actively when compensated cardiac hypertrophy develops into decompensated heart failure. Wang, Y., et al., "Cardiac muscle cell hypertrophy and apoptosis induced by distinct members of the p38 mitogen-activated protein kinase family", *J Biol Chem.*, 273:2161-2168 (1998).

[7] Inhibition of p38 MAPKs has been investigated as a possible method for treating various cardiovascular conditions. It has been reported, for example, that inhibition of p38 activity improved cardiac function after myocardial ischemia and reperfusion. *See, e.g.*, Ma, X.L., et al., "Inhibition of p38 mitogen-activated protein kinase decreases cardiomyocyte apoptosis and improves cardiac function after myocardial ischemia and reperfusion", *Circulation*, 99:1685-1691 (1999). It also has been reported that *trans*-1-(4-hydroxycyclohexyl)-4-(4-fluorophenyl methoxypyridimidin-4-yl)imidazole (reported to be a specific p38 inhibitor) protected against hypertensive end-organ damage, reduced plasma tumor necrosis factor (TNF-α), and improved survival in a rat model of cardiac hypertrophy and dysfunction. *See, e.g.*, Behr T.M., et al. And it has been reported that p38 MAPKs are associated with myocardial apoptosis, and that p38 inhibition reduced post-ischemic myocardial apoptosis. *See, e.g.*, Ma, X.L., et al. *See also*, Xia, Z., et al., "Opposing effects of ERK and JNK-p38 MAP kinases on apoptosis", *Science*, 270:1326-1331 (1995).

[8] In U.S. Patent No. 6,093,742, Salituro et al. discuss generally the use of various oxo, thioxo, and imino compounds that purportedly inhibit p38 kinase to treat, *inter alia*, myocardial ischemia, heart attack, cardiac hypertrophy, and thrombin-induced platelet aggregation. And, in U.S. Patent No. 6,130,235, Mavunkel et al. discuss generally the use of various piperidinyl and piperazinyl compounds that purportedly inhibit p38 kinase to treat, *inter alia*, coronary artery disease; congestive heart failure;

cardiomyopathy; myocarditis; vasculitis; restinosis, such as restinosis that occurs following coronary angioplasty; valvular disease; atherosclerosis; heart failure characterized by ischemia and reperfusion injury; conditions associated with cardiopulmonary bypass; and coronary artery bypass graft.

[9] Other patent references discuss use of substituted-pyrazole p38-kinase inhibitors to treat cardiovascular conditions. *See, e.g.*, Anantanarayan et al., PCT Application No. PCT/US98/10807; and U.S. Patent Nos. 5,932,576; 6,087,496; and 6,335,336. *See also, e.g.*, Hanson, et al., PCT Application No. PCT/US98/11684; and U.S. Patent Nos. 6,087,381 and 6,503,930. *See also, e.g.*, Weier, et al., PCT Application No. PCT/US99/07036; and U.S. Patent No. 6,509,361. *See also, e.g.*, Anantanarayan, et al., PCT Application No. PCT/US98/10436. *See also, e.g.*, Anantanarayan et al., U.S. Patent No. 6,514,977 and 6,423,713. *See also, e.g.*, Anantanarayan et al., PCT Application No. PCT/US99/26007; and U.S. Patent No. 6,525,059. *See also, e.g.*, Benson, et al., U.S. Patent Application Serial No. 60/386,415 (filed June 5, 2002).

[10] Various combination therapies for treating cardiovascular diseases have been described in the literature.

[11] For example, in PCT Application No. PCT/US99/27946, Keller et al. disclose combinations comprising ileal bile acid transport ("IBAT") inhibitors or cholesteryl ester transport protein ("CTEP") inhibitors with other agents to treat various cardiovascular conditions.

[12] In PCT Application No. PCT/US00/31263, Williams et al. disclose combinations comprising epoxy-steroidal aldosterone antagonists with other agents to treat hypertension and other various cardiovascular conditions.

[13] In U.S. Patent No. 6,410,524, Perez et al. disclose combinations comprising ACE inhibitors, aldosterone antagonists, and diuretics to treat various circulatory disorders.

[14] Combinations of IBAT inhibitors with HMG CoA reductase inhibitors useful for the treatment of cardiovascular disease are disclosed by Keller, et al. in U.S. Patent No. 6,268,392 and Reitz et al. in PCT Patent Publication No. 98/40375.

[15] A combination therapy of fluvastatin and niceritrol is described by J. Sasaki et al. (*Int. J. Clin. Pharm. Ther.*, 33(7), 420-26 (1995)). Those researchers conclude that

the combination of fluvastatin with niceritrol "at a dose of 750 mg/day dose does not appear to augment or attenuate beneficial effects of fluvastatin."

[16] Cashin-Hemphill et al. (*J. Am. Med. Assoc.*, 264(23), 3013-17 (1990)) report beneficial effects of a combination therapy of colestipol and niacin on coronary atherosclerosis. The described effects include non-progression and regression in native coronary artery lesions.

[17] A combination therapy of acipimox and simvastatin has been reported to show beneficial HDL effects in patients having high triglyceride levels (N. Hoogerbrugge et al., *J. Internal Med.*, 241, 151-55 (1997)).

[18] Sitostanol ester margarine and pravastatin combination therapy is described by H. Gylling et al. (*J. Lipid Res.*, 37, 1776-85 (1996)). That therapy is reported to simultaneously inhibit cholesterol absorption and lower LDL cholesterol significantly in non-insulin-dependent diabetic men.

[19] Brown et al. (*New Eng. J. Med.*, 323(19), 1289-1339 (1990)) describe a combination therapy of lovastatin and colestipol which reportedly reduces atherosclerotic lesion progression and increase lesion regression relative to lovastatin alone.

[20] In PCT Patent Publication No. WO 99/11260, Scott describes combinations of atorvastatin (an HMG CoA reductase inhibitor) with an antihypertensive agent for the treatment of angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia, and symptoms of cardiac risk.

[21] In PCT Patent Publication No. WO 96/40255, Egan et al. describe a combination therapy of an angiotensin II antagonist and an epoxy-steroidal aldosterone antagonist. The epoxy-steroidal aldosterone antagonists in the Egan application include eplerenone.

[22] In PCT Patent Publication No. WO 02/09759, Rocha et al. describe a combination therapy of an aldosterone antagonist and cyclooxygenase-2 inhibitor for the treatment of inflammation-related cardiovascular disorders.

[23] In PCT Patent Publication No. WO 02/09760, Alexander et al. describe a combination therapy of an epoxy-steroidal aldosterone antagonist and beta-adrenergic antagonist for treating congestive heart failure.

[24] In PCT Patent Publication No. WO 02/09761, Schuh describes a combination therapy of an epoxy-steroidal aldosterone antagonist and calcium channel blocker for treating congestive heart failure.

[25] In PCT Patent Publication No. WO 02/09683, Williams et al. describe, *inter alia*, combination therapies of an aldosterone antagonist and, for example, an ACE inhibitor or diuretic to treat inflammation-related disorders, including cardiovascular disorders.

[26] In PCT Patent Publication No. WO 01/95893, Williams et al. describe, *inter alia*, combination therapies of an epoxy-steroidal aldosterone antagonist and, for example, an ACE inhibitor or diuretic to treat aldosterone-mediated pathogenic effects, including cardiovascular disorders.

[27] Despite the foregoing, heart disease continues to be one of the leading causes of human healthcare costs and death in the world, and the leading cause of human death in the United States and other countries. Thus, there continues to be a need for effective methods and compositions to treat cardiovascular diseases. The following disclosure describes methods and compositions addressing this need.

SUMMARY OF THE INVENTION

[28] This invention is directed, in part, to a method for treating a pathological cardiovascular condition or a condition associated with a cardiovascular condition. Such a method is typically suitable for use with mammals, such as humans, other primates (*e.g.*, monkeys, chimpanzees. etc.), companion animals (*e.g.*, dogs, cats, horses. etc.), farm animals (*e.g.*, goats, sheep, pigs, cattle, etc.), laboratory animals (*e.g.*, mice, rats, etc.), and wild and zoo animals (*e.g.*, wolves, bears, deer, etc.).

[29] Briefly, therefore, this invention is directed, in part, to a method for treating a pathological condition in a mammal.

[30] In some embodiments, the method comprises administering to the mammal a first amount of a compound that comprises a substituted-pyrazole that inhibits p38-kinase activity. The method also comprises administering to the mammal a second amount of a compound that inhibits ACE activity. Here, the first and second amounts together comprise a therapeutically-effective amount of the compounds.

[31] In some embodiments, the method comprises administering to the mammal a first amount of a compound that inhibits p38-kinase activity. The method also comprises administering to the mammal a second amount of a compound that inhibits ACE activity. The first and second amounts together comprise a therapeutically-effective amount of the compounds. Here, the pathological condition comprises a cardiovascular disease, glomerulosclerosis, end-stage renal disease, acute renal failure, diabetic nephropathy, reduced renal blood flow, increased glomerular filtration fraction, decreased glomerular filtration rate, decreased creatine clearance, renal arteriopathy, ischemic renal lesions, vascular damage in the kidney, vascular inflammation in the kidney, malignant nephrosclerosis, thrombotic vascular disease, proliferative arteriopathy, atherosclerosis, decreased vascular compliance, retinopathy, neuropathy, edema, or insulinopathy.

[32] This invention also is directed, in part, to a composition (particularly a pharmaceutical composition or medicament). The composition comprises a first amount of a compound that comprises a compound that inhibits p38-kinase activity. The composition also comprises a second amount of a compound that inhibits ACE activity.

[33] This invention also is directed, in part, to a kit. The kit comprises a first dosage form comprising a compound that inhibits p38-kinase activity. The kit also comprises a second dosage form that inhibits ACE activity.

[34] This invention also is directed, in part, to a use of a p38-kinase inhibiting compound and an ACE inhibiting compound to make a medicament for treating a pathological condition in a mammal. The medicament comprises a first amount of the p38-kinase inhibiting compound, and a second amount of the ACE inhibiting compound. These first and second amounts of the compounds together comprise a therapeutically-effective amount of the compounds.

[35] In some embodiments directed to making a medicament, the p38-kinase inhibiting compound comprises a substituted pyrazole.

[36] In some embodiments directed to making a medicament, the pathological condition comprises a cardiovascular disease, glomerulosclerosis, end-stage renal disease, acute renal failure, diabetic nephropathy, reduced renal blood flow, increased glomerular filtration fraction, decreased glomerular filtration rate, decreased creatine clearance, renal arteriopathy, ischemic renal lesions, vascular damage in the kidney, vascular inflammation in the kidney, malignant nephrosclerosis, thrombotic vascular disease, proliferative

arteriopathy, atherosclerosis, decreased vascular compliance, retinopathy, neuropathy, edema, or insulinopathy.

[37] Further benefits of Applicants' invention will be apparent to one skilled in the art from reading this specification.

BRIEF DESCRIPTION OF THE DRAWINGS

[38] **Figure 1** compares the mean systolic blood pressure for each of the groups of rats at the end of the 12-week study.

[39] **Figure 2** compares the mean ejection fraction for each of the groups of rats at the end of the 12-week study.

[40] **Figure 3** compares the mean stroke volume for each of the groups of rats at the end of the 12-week study.

[41] **Figure 4** compares the mean left ventricular ("LV") end diastolic area and left ventricular end systolic area for each of the groups of rats at the end of the 12-week study.

[42] **Figure 5** compares the mean left ventricular end diastolic volume and left ventricular end systolic volume for each of the groups of rats at the end of the 12-week study.

[43] **Figure 6** compares the mean left ventricular mass and heart weight (normalized by tibial length) for each of the groups of rats at the end of the 12-week study.

[44] **Figure 7** compares the mean proteinurea (averaged over 24 hours) for each of the groups of rats at the end of the 12-week study.

[45] **Figure 8** compares the mean serum concentration of TNF-α for each of the groups of rats at the end of the 12-week study.

[46] **Figure 9** compares the mean serum concentration of TNFR1 and TNFR2 for each of the groups of rats at the end of the 12-week study.

[47] **Figure 10** compares the mean plasma concentration of osteopontin for each of the groups of rats at the end of the 12-week study.

[48] **Figure 11** shows cardiac p38 activity of representative animals from each group of rats at the end of the 12-week study.

[49] **Figure 12** shows combined MMP-2 and MMP-9 activity in left ventricular tissue of representative animals from each group of rats at the end of the 12-week study.

The figure shows both the actual gelatin zymography results, as well as a chart that quantifies those results into relative densitometric units.

[50] **Figure 13** compares the mean MMP-2, MMP-3, MMP-13, and MMP-14 expression at the end of the 12-week study.

[51] **Figure 14** compares the mean TIMP-1, TIMP-2, and TIMP-4 expression at the end of the 12-week study.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[52] This detailed description of preferred embodiments is intended only to acquaint others skilled in the art with Applicants' invention, its principles, and its practical application so that others skilled in the art may adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This detailed description and its specific examples, while indicating preferred embodiments of this invention, are intended for purposes of illustration only. This invention, therefore, is not limited to the preferred embodiments described in this specification, and may be variously modified.

[53] It has been discovered that administration of one or more p38-kinase inhibitors, particularly in combination with one or more angiotensin-converting-enzyme inhibitors, generally provides an effective treatment for a variety of cardiovascular conditions. Such effectiveness may be realized in, for example, efficacy, potency, dosing requirements, and/or reduced side effects. The term "cardiovascular condition" is used broadly in this application, and includes, for example, hypertension, heart failure (such as congestive heart failure (*i.e.*, "CHF"), or heart failure following myocardial infarction), arrhythmia, diastolic dysfunction (such as left ventricular diastolic dysfunction, diastolic heart failure, or impaired diastolic filling), systolic dysfunction, ischemia (such as myocardial ischemia), cardiomyopathy (such as hypertrophic cardiomyopathy and dilated cardiomyopathy), sudden cardiac death, myocardial fibrosis, vascular fibrosis, impaired arterial compliance, myocardial necrotic lesions, vascular damage in the heart, vascular inflammation in the heart, myocardial infarction ("MI") (including both acute post-MI and chronic post-MI conditions), coronary angioplasty, left ventricular hypertrophy, decreased ejection fraction, coronary thrombosis, cardiac lesions, vascular wall hypertrophy in the

heart, endothelial thickening, myocarditis, and coronary artery disease (such as fibrinoid necrosis of coronary arteries).

[54] It also has been discovered that administration of one or more p38-kinase inhibitors, particularly in combination with one or more angiotensin-converting-enzyme inhibitors, generally provides an effective treatment for a variety of conditions that are associated (either directly or indirectly) with hypertension, heart failure, and/or other cardiovascular conditions. Such secondary conditions include, for example, renal dysfunctions, cerebrovascular diseases, vascular diseases generally, retinopathy, neuropathy (such as peripheral neuropathy), edema, endothelial dysfunction, and insulinopathy (including complications arising from insulinopathy). Examples of renal dysfunctions include glomerulosclerosis, end-stage renal disease, acute renal failure, diabetic nephropathy, reduced renal blood flow, increased glomerular filtration fraction, proteinuria, decreased glomerular filtration rate, decreased creatine clearance, microalbuminuria, renal arteriopathy, ischemic lesions, vascular damage in the kidney, vascular inflammation in the kidney, and malignant nephrosclerosis (such as ischemic retraction, thrombonecrosis of capillary tufts, arteriolar fibrinoid necrosis, and thrombotic microangiopathic lesions affecting glomeruli and microvessels). Examples of cerebrovascular diseases include stroke. Examples of vascular diseases include thrombotic vascular disease (such as mural fibrinoid necrosis, extravasation and fragmentation of red blood cells, and luminal and/or mural thrombosis), proliferative arteriopathy (such as swollen myointimal cells surrounded by mucinous extracellular matrix and nodular thickening), atherosclerosis, decreased vascular compliance (such as pathological vascular stiffness and/or reduced ventricular compliance), and endothelial dysfunction. Examples of edema include peripheral tissue edema and lung congestion. Examples of insulinopathies include insulin resistance, Type I diabetes mellitus, Type II diabetes mellitus, glucose sensitivity, pre-diabetic state, and syndrome X.

[55] In some embodiments, the pathological condition comprises a cardiovascular disease, renal dysfunction, edema, a cerebrovascular disease, or an insulinopathy.

[56] In some embodiments, the pathological condition comprises a cardiovascular disease, stroke, or type II diabetes.

[57] In some embodiments, the pathological condition comprises hypertension, heart failure, left ventricular hypertrophy, or stroke.

[58] In some embodiments, the pathological condition comprises a cardiovascular disease.

[59] In some embodiments, the pathological condition comprises hypertension.

[60] In some embodiments, the pathological condition comprises heart failure, arrhythmia, diastolic dysfunction, systolic dysfunction, ischemia, cardiomyopathy, sudden cardiac death, myocardial fibrosis, vascular fibrosis, impaired arterial compliance, myocardial necrotic lesions, vascular damage in the heart, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, vascular wall hypertrophy in the heart, or endothelial thickening.

[61] In some embodiments, the pathological condition comprises heart failure.

[62] In some embodiments, the pathological condition comprises acute heart failure.

[63] In some embodiments, the pathological condition comprises acute post-myocardial-infarction heart failure.

[64] In some embodiments, the pathological condition comprises chronic heart failure.

[65] In some embodiments, the pathological condition comprises chronic post-myocardial-infarction heart failure.

[66] In some embodiments, the pathological condition comprises hypertension-driven heart failure.

[67] In some embodiments, the pathological condition comprises sudden cardiac death.

[68] In some embodiments, the pathological condition comprises vascular inflammation in the heart.

[69] In some embodiments, the pathological condition comprises coronary angioplasty.

[70] In some embodiments, the pathological condition comprises coronary thrombosis.

[71] In some embodiments, the pathological condition comprises cardiac lesions.

[72] In some embodiments, the pathological condition comprises myocarditis.

[73] In some embodiments, the pathological condition comprises coronary artery disease, such as fibrinoid necrosis of coronary arteries.

[74] In some embodiments, the pathological condition comprises renal dysfunction.

[75] In some embodiments, the pathological condition comprises a cerebrovascular disease.

[76] In some embodiments, the pathological condition comprises an insulinopathy.

[77] In some embodiments, the patient is a companion animal. In some such embodiments, for example, the companion animal is a dog (or "canine"), and the pathological condition comprises heart failure.

[78] It should be recognized that a condition treatable by methods of this invention may exist as a continuous or intermittent condition in a subject. The condition also may be a chronic or acute condition.

A. Examples of p38-Kinase Inhibitors

[79] In some preferred embodiments, the p38-kinase inhibitor comprises a substituted pyrazole.

[80] In some embodiments wherein the p38-kinase inhibitor comprises a substituted pyrazole, the p38-kinase inhibitor is selected from the group consisting of p38-kinase inhibitors disclosed by Anantanarayan et al. in WIPO Int'l Application No. PCT/US98/10807 (filed May 22, 1998; published November 26, 1998 as Publ. No. WO 98/52937); U.S. Patent No. 5,932,576 (issued August 3, 1999; filed May 22, 1998 as U.S. Application No. 09/083,923); U.S. Patent No. 6,087,496 (issued July 11, 2000; filed April 1, 1999 as U.S. Application No. 09/283,718); U.S. Patent No. 6,335,336 (issued January 1, 2002; filed April 28, 2000 as U.S. Application No. 09/561,423); and U.S. Patent Application No. 10/024,071 (filed December 18, 2001) (all of which are incorporated by reference into this patent).

[81] In some embodiments wherein the p38-kinase inhibitor comprises a substituted pyrazole, the p38-kinase inhibitor is selected from the group consisting of p38-kinase inhibitors disclosed by Hanson, et al. in WIPO Int'l Application No.

PCT/US98/11684 (filed May 22, 1998; published November 26, 1998 as Publ. No. WO 98/52941); U.S. Patent No. 6,087,381 (issued July 11, 2000; filed May 22, 1998 as U.S. Application No. 09/083,724); U.S. Patent No. 6,503,930 (issued January 7, 2003; filed march 31, 2000 as U.S. Application No. 09/540,464); and U.S. Patent Application No. 10/267,650 (filed October 9, 2002) (all of which are incorporated by reference into this patent).

[82] In some embodiments wherein the p38-kinase inhibitor comprises a substituted pyrazole, the p38-kinase inhibitor is selected from the group consisting of p38-kinase inhibitors disclosed by Weier, et al. in WIPO Int'l Application No. PCT/US99/07036 (filed May 12, 1999; published November 18, 1999 as Publ. No. WO 99/58523); U.S. Patent No. 6,509,361 (issued January 21, 2003; filed February 21, 2001 as U.S. Application No. 09/674,653); and U.S. Patent Application No. 10/322,039 (filed December 17, 2002) (all of which are incorporated by reference into this patent).

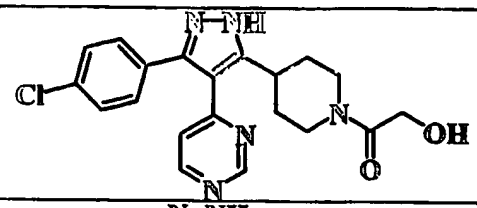
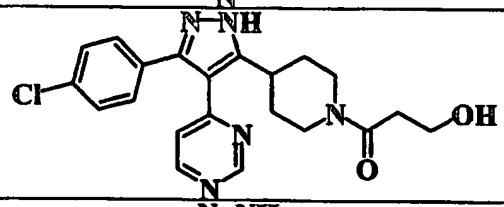
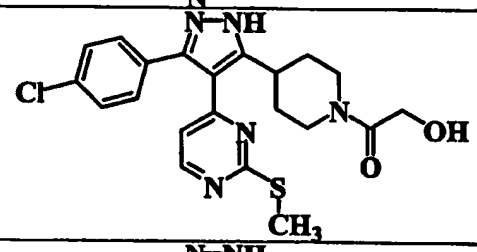
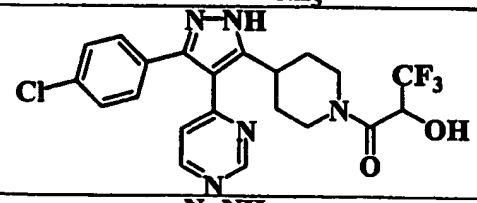
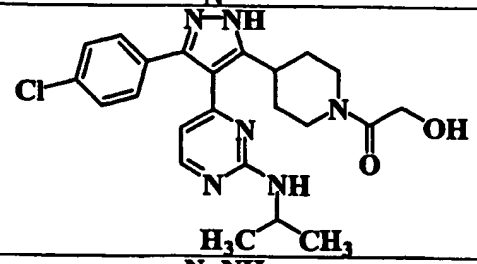
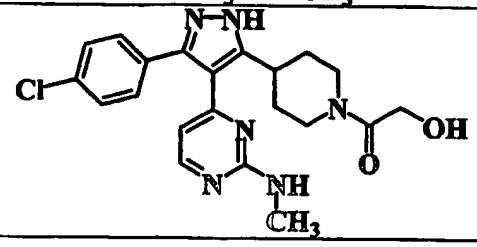
[83] In some embodiments wherein the p38-kinase inhibitor comprises a substituted pyrazole, the p38-kinase inhibitor is selected from the group consisting of p38-kinase inhibitors disclosed by Anantanarayan, et al. in WIPO Int'l Application No. PCT/US98/10436 (filed May 22, 1998; published November 26, 1998 as Publ. No. WO 98/52940) (incorporated by reference into this patent).

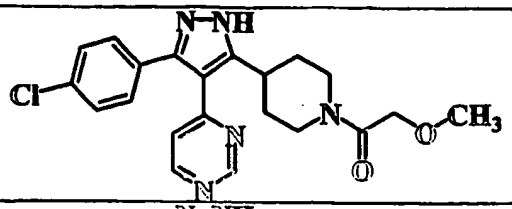
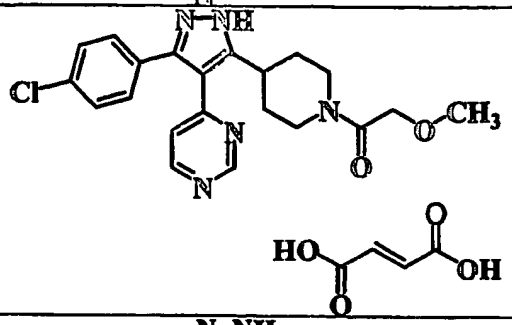
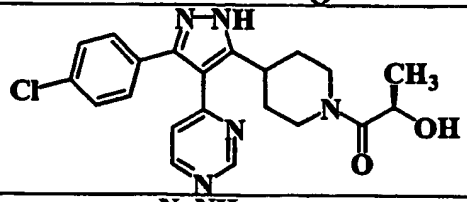
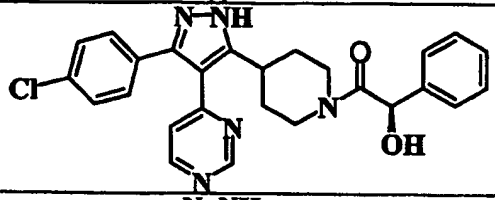
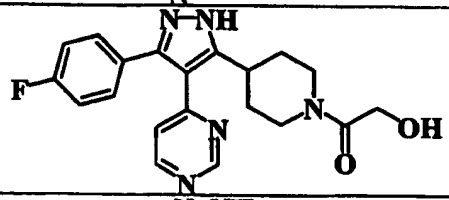
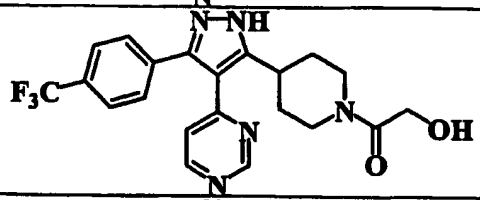
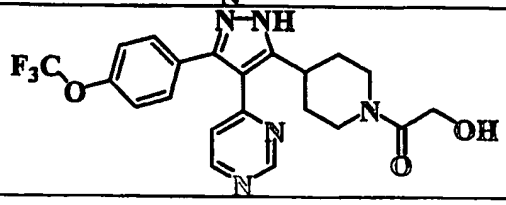
[84] In some embodiments wherein the p38-kinase inhibitor comprises a substituted pyrazole, the p38-kinase inhibitor is selected from the group consisting of p38-kinase inhibitors disclosed by Anantanarayan et al. in U.S. Patent No. 6,514,977 (issued February 4, 2003; filed May 22, 1998 as U.S. Application No. 09/083,670); U.S. Patent No. 6,423,713 (issued July 23, 2002; filed July 31, 2001 as U.S. Application No. 09/918,481); and U.S. Patent Application No. 10/114,297 (filed April 2, 2002) (all of which are incorporated by reference into this patent).

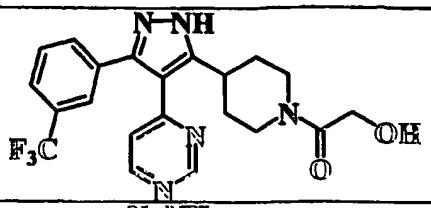
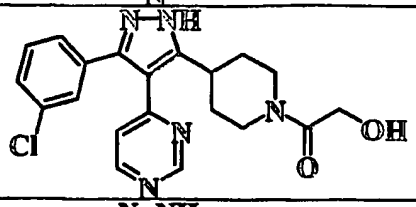
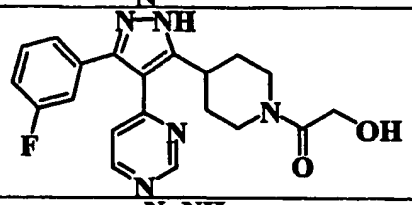
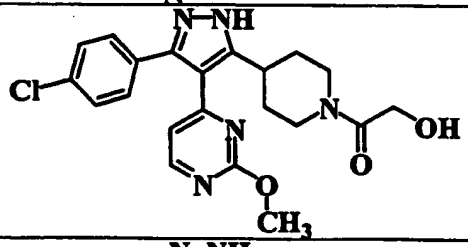
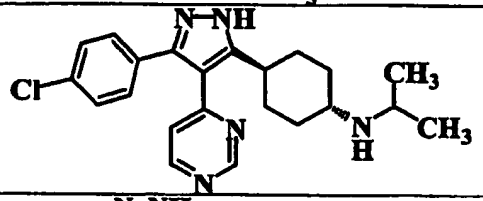
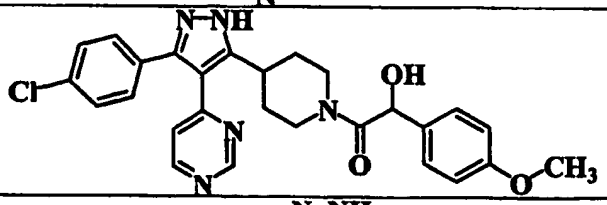
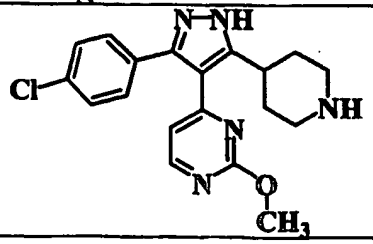
[85] In some embodiments wherein the p38-kinase inhibitor comprises a substituted pyrazole, the p38-kinase inhibitor is selected from the group consisting of p38-kinase inhibitors disclosed by Anantanarayan et al. in WIPO Int'l Application No. PCT/US99/26007 (filed November 17, 1999; published June 2, 2000 as Publ. No. WO 00/31063); U.S. Patent No. 6,525,059 (issued February 25, 2003; filed February 24, 2000 as U.S. Application No. 09/513,351); and U.S. Patent Application No. 10/021,780 (filed

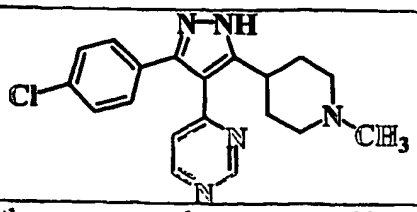
December 7, 2001) (all of which are incorporated by reference into this patent). Those p38-kinase inhibitors include, for example, the compounds shown in **Table 1**:

Table 1

Compound Number	Compound
P-1	
P-2	
P-3	
P-4	
P-5	
P-6	

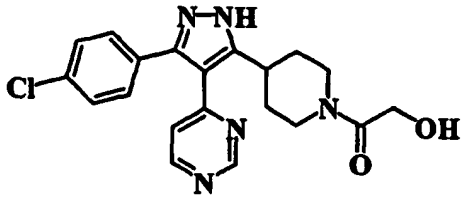
Compound Number	Compound
P-7	
P-8	
P-9	
P-10	
P-11	
P-12	
P-13	

Compound Number	Compound
P-14	
P-15	
P-16	
P-17	
P-18	
P-19	
P-20	

Compound Number	Compound
P-21	

In some preferred embodiments, these compounds are prepared by a process disclosed by Allen et al. in U.S. Patent Application No. 10/254,445 (filed September 25, 2002); and PCT Publication No. WO 03/026663 (both of which are incorporated by reference into this patent). *See also*, U.S. Patent Application No. 10/456,933 (filed June 5, 2003); and PCT Patent Publication No. WO 03/104223 (both of which are incorporated by reference into this patent).

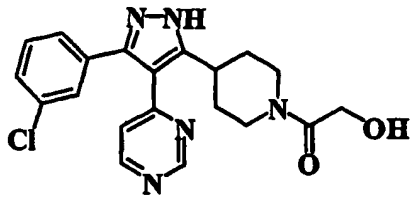
[86] In some embodiments wherein the p38-kinase inhibitor comprises a substituted pyrazole, the p38-kinase inhibitor corresponds in structure to **Formula P-1**:



P-1.

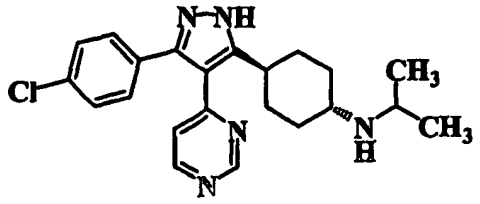
In some preferred embodiments, this compound comprises a crystalline form disclosed by Allen et al. in U.S. Patent Application No. 10/254,697 (filed September 25, 2002); and PCT Application No. PCT/US02/30538 (filed September 25, 2002) (both of which are incorporated by reference into this patent).

[87] In some embodiments wherein the p38-kinase inhibitor comprises a substituted pyrazole the p38-kinase inhibitor corresponds in structure to **Formula P-15**:



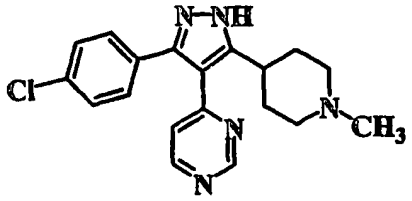
P-15.

[88] In some embodiments wherein the p38-kinase inhibitor comprises a substituted pyrazole the p38-kinase inhibitor corresponds in structure to **Formula P-18**:



P-18.

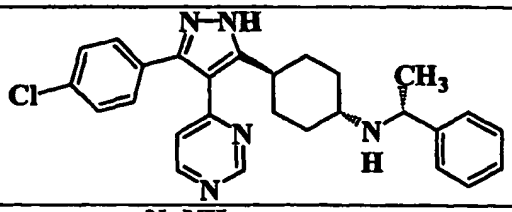
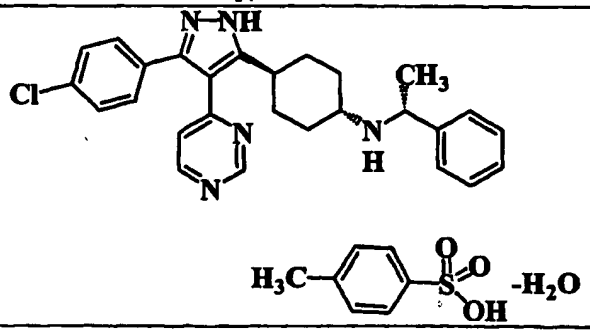
[89] In some embodiments wherein the p38-kinase inhibitor comprises a substituted pyrazole the p38-kinase inhibitor corresponds in structure to **Formula P-21**:

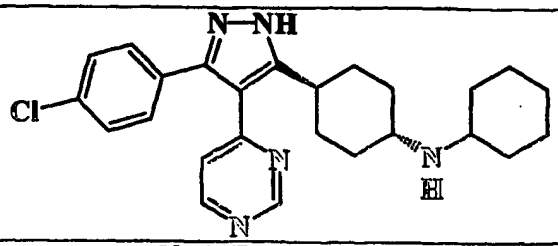
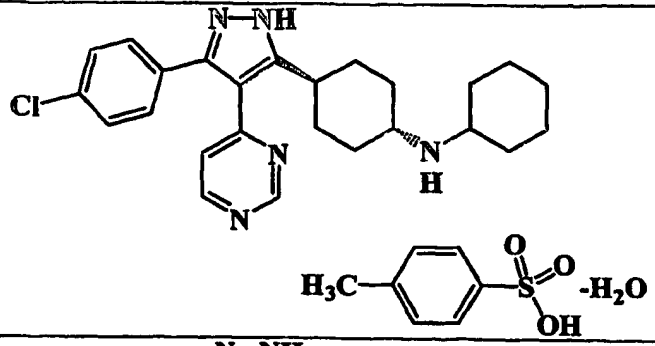
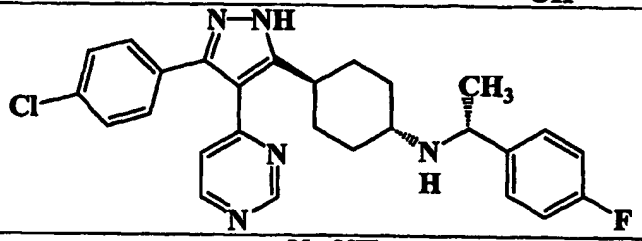
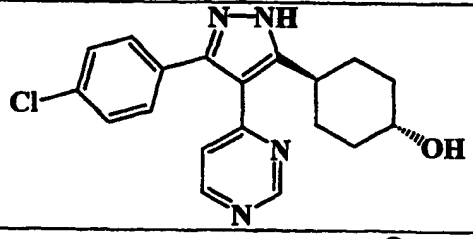
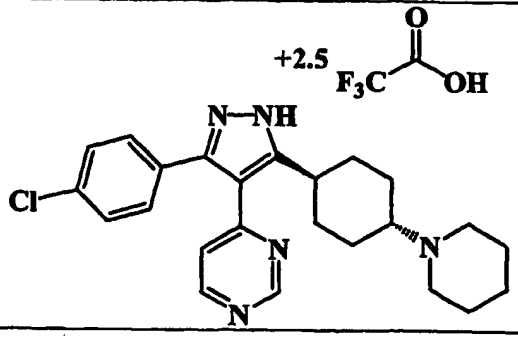


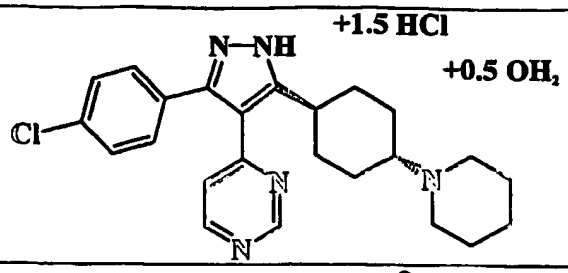
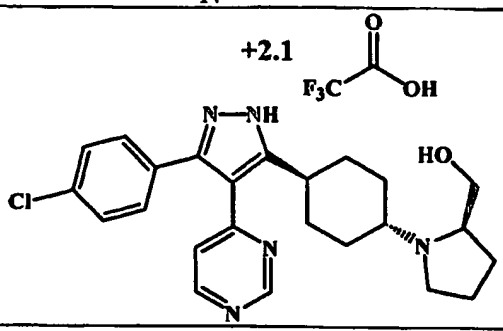
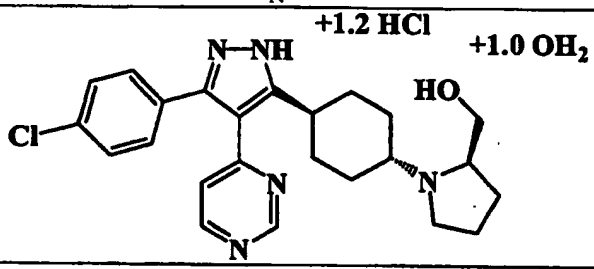
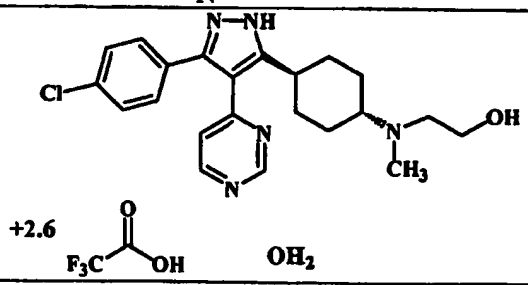
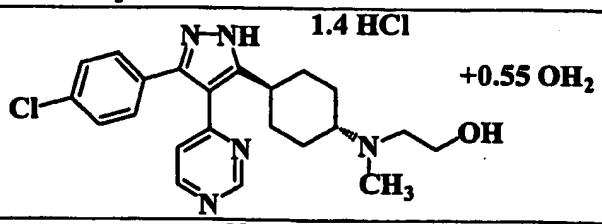
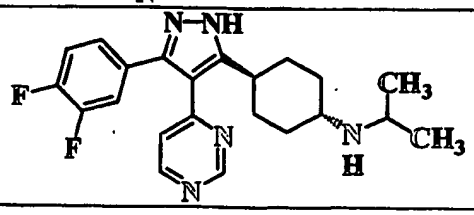
P-21.

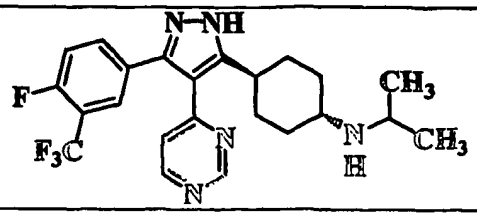
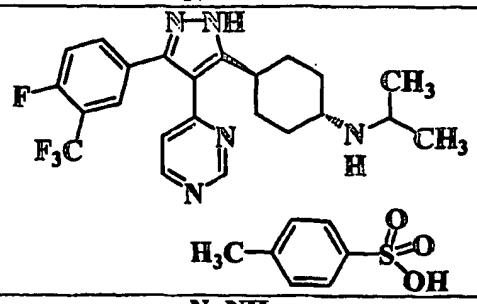
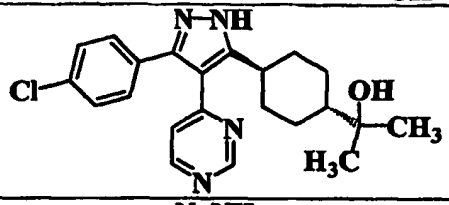
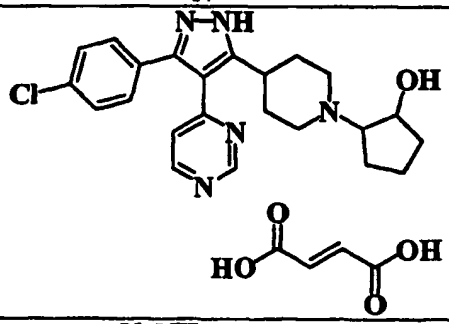
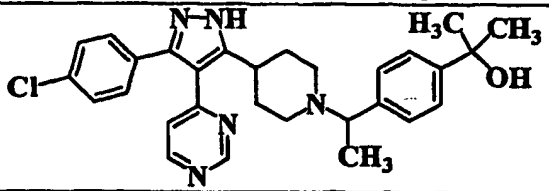
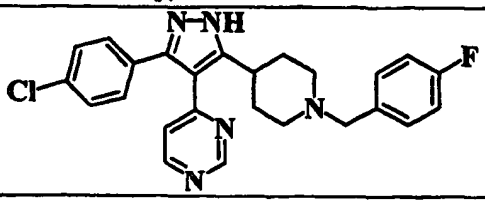
[90] In some embodiments wherein the p38-kinase inhibitor comprises a substituted pyrazole, the p38-kinase inhibitor is selected from the group of p38-kinase inhibitors disclosed by Benson, et al. in U.S. Patent Application Serial No. 60/386,415 (filed June 5, 2002) (incorporated by referenced into this patent). Those p38-kinase inhibitors include, for example, the compounds shown in **Table 2**:

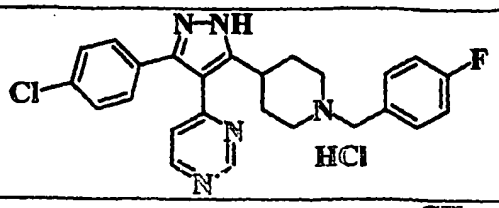
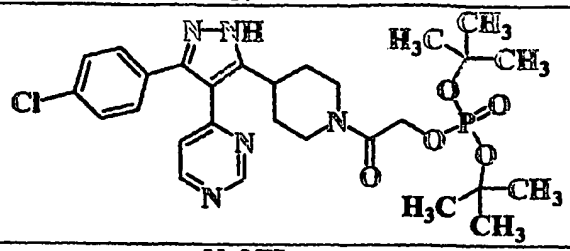
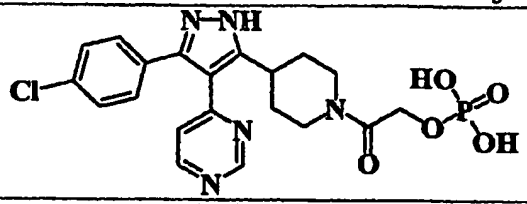
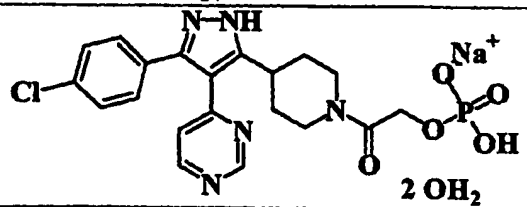
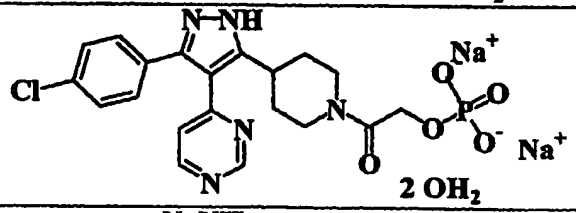
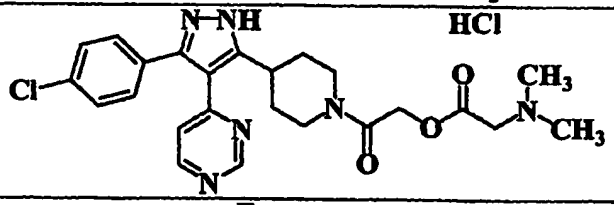
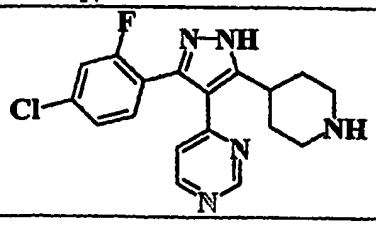
Table 2

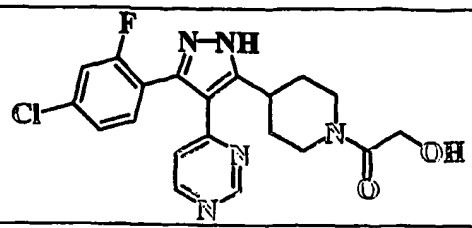
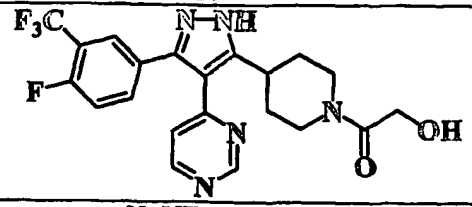
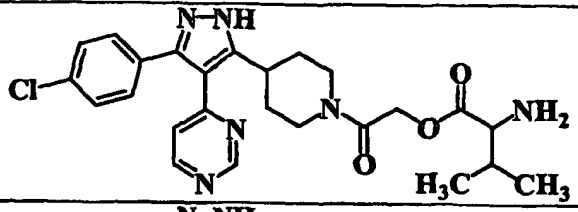
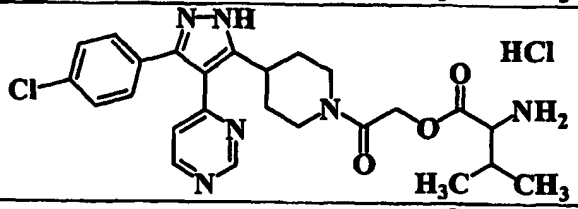
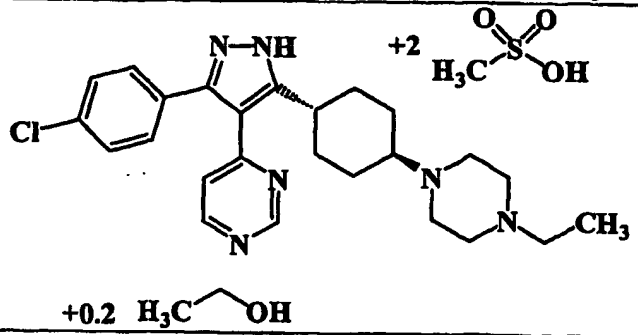
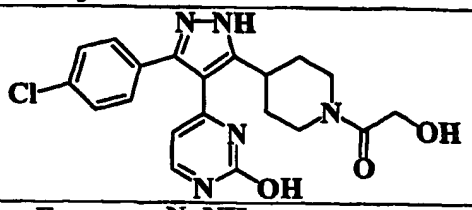
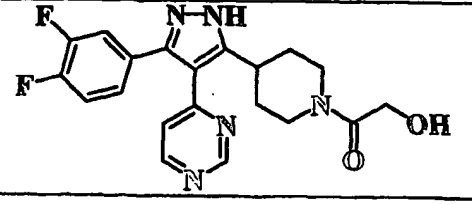
Compound Number	Compound
P-22	
P-23	

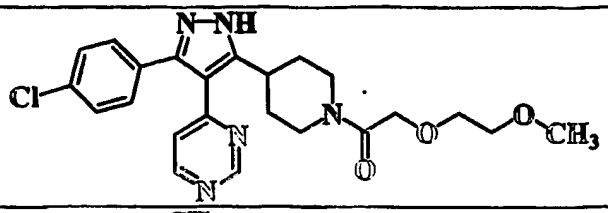
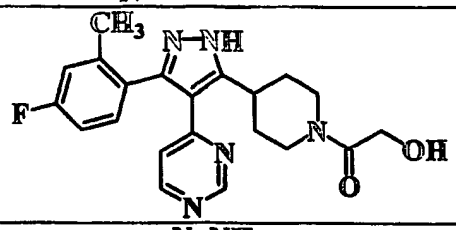
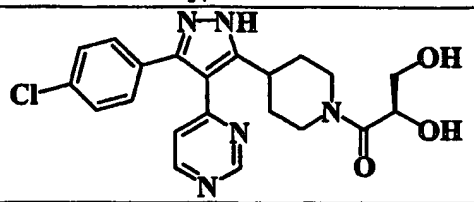
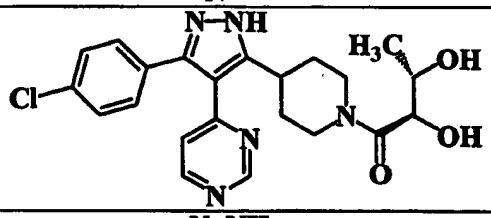
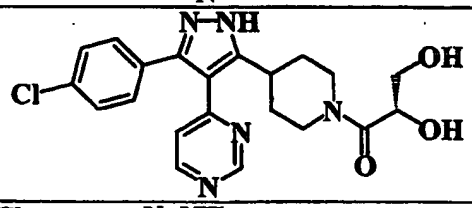
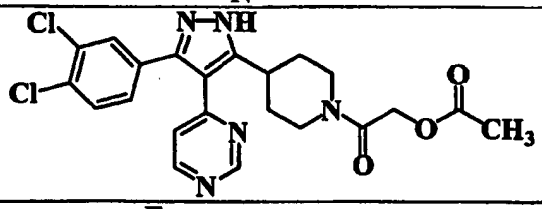
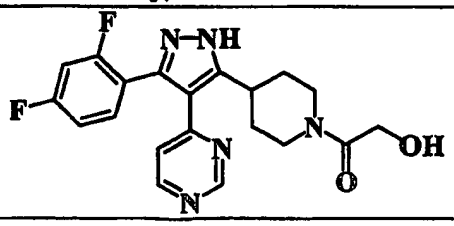
Compound Number	Compound
P-24	
P-25	
P-26	
P-27	
P-28	

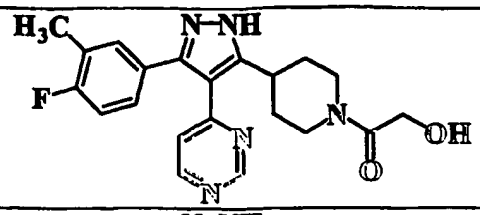
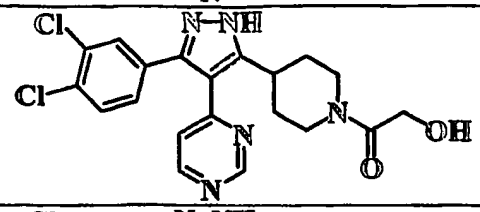
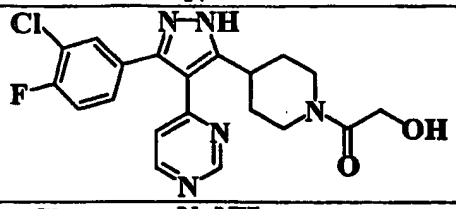
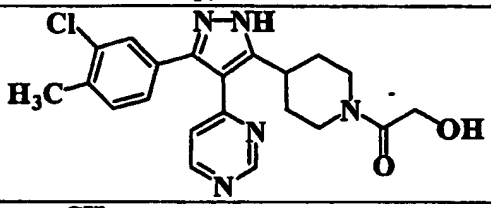
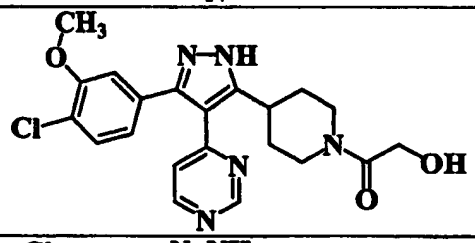
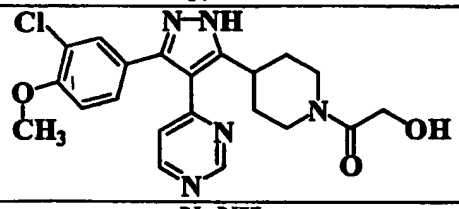
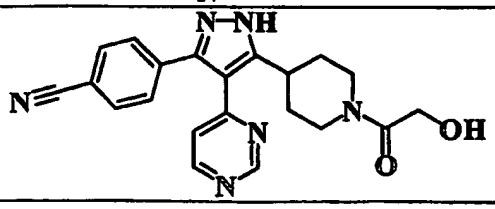
Compound Number	Compound
P-29	
P-30	
P-31	
P-32	
P-33	
P-34	

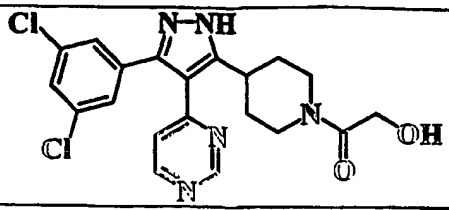
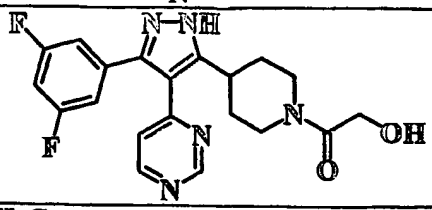
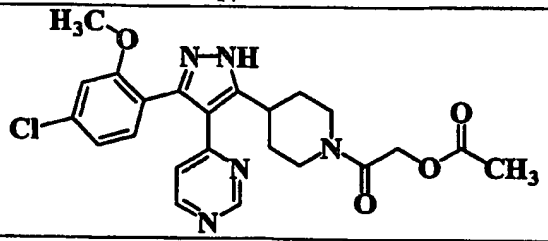
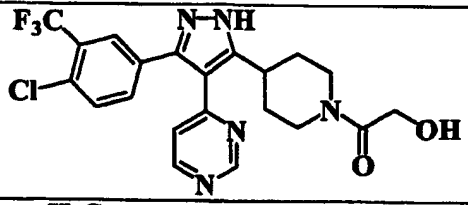
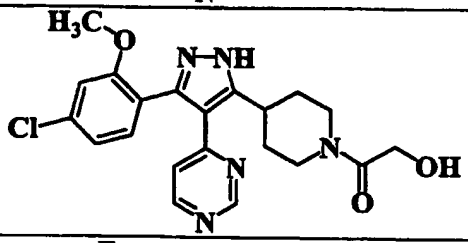
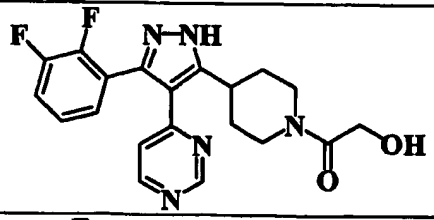
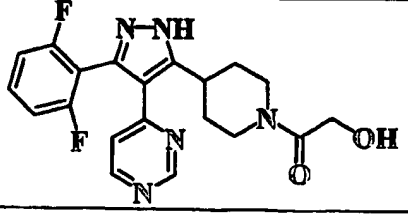
Compound Number	Compound
P-35	
P-36	
P-37	
P-38	
P-39	
P-40	

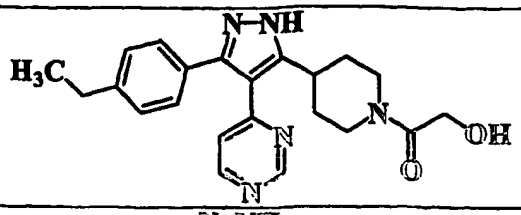
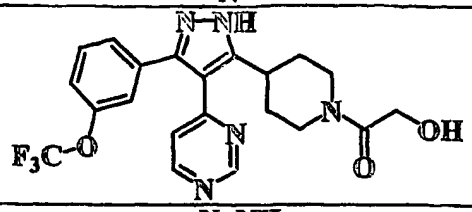
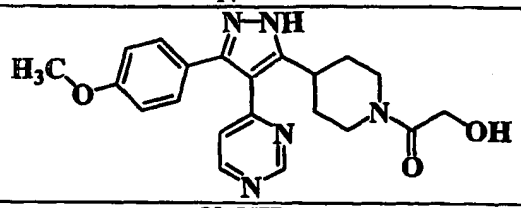
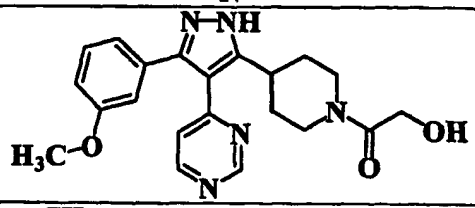
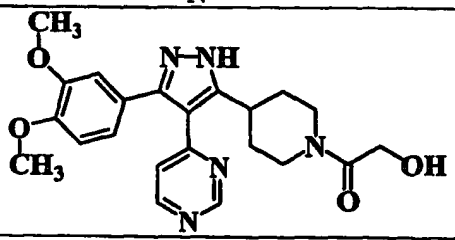
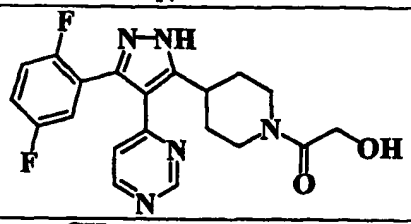
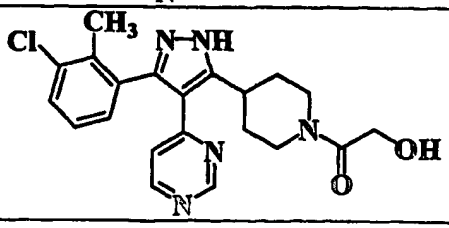
Compound Number	Compound
P-41	
P-42	
P-43	
P-44	
P-45	
P-46	
P-47	

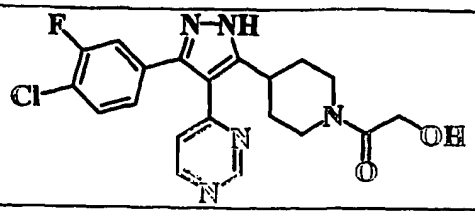
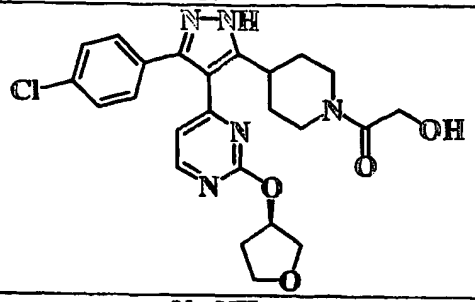
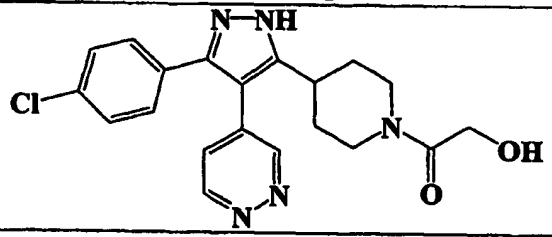
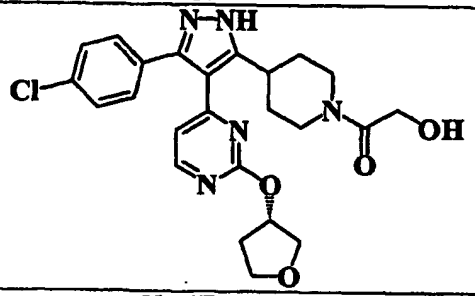
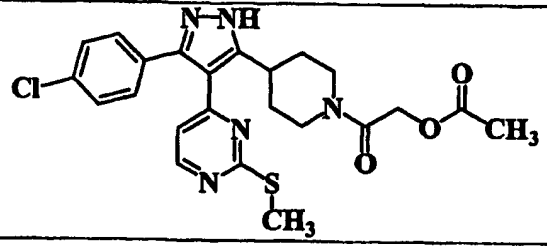
Compound Number	Compound
P-48	
P-49	
P-50	
P-51	
P-52	
P-53	
P-54	

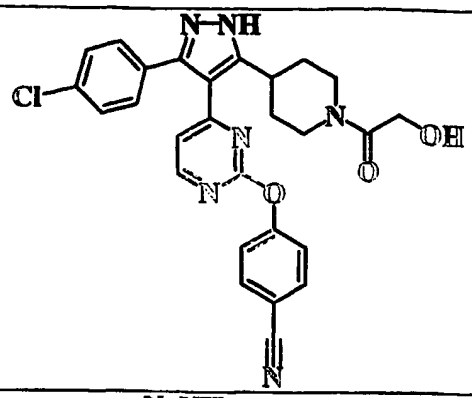
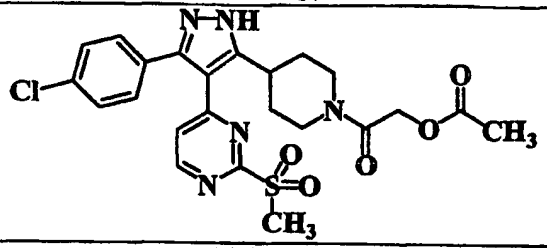
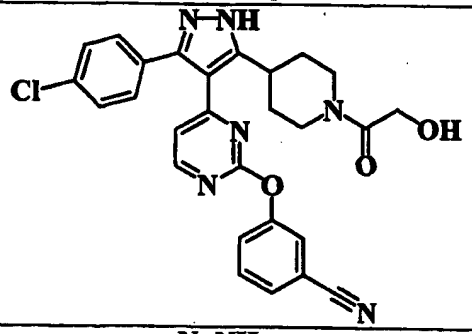
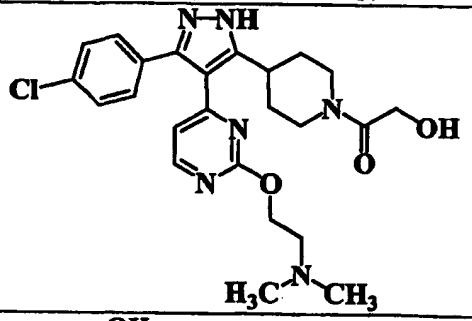
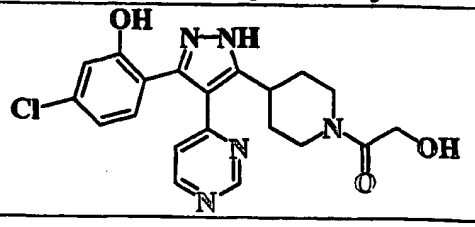
Compound Number	Compound
P-55	
P-56	
P-57	
P-58	
P-59	
P-60	
P-61	

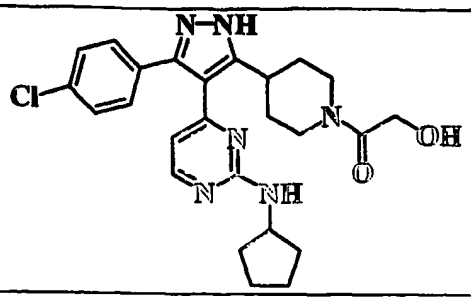
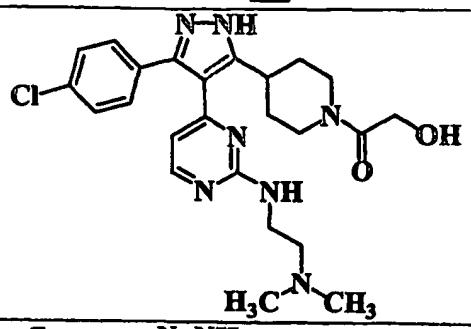
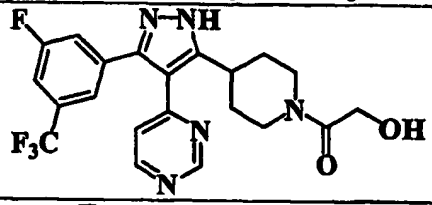
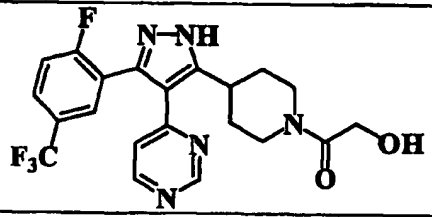
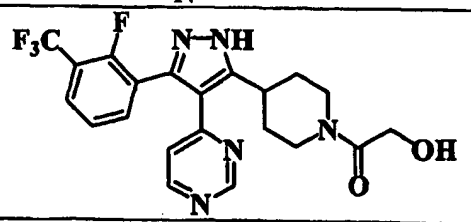
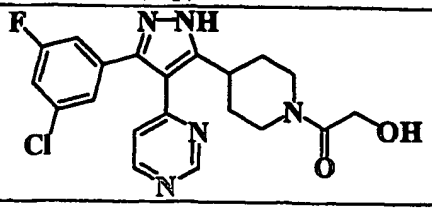
Compound Number	Compound
P-62	
P-63	
P-64	
P-65	
P-66	
P-67	
P-68	

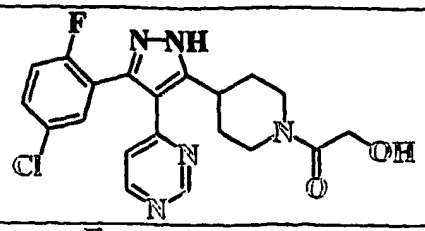
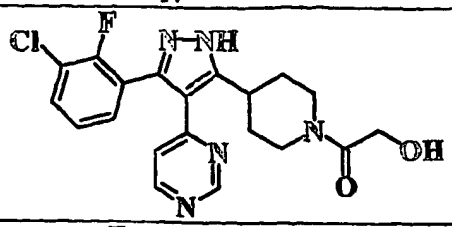
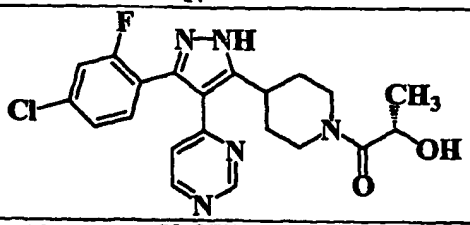
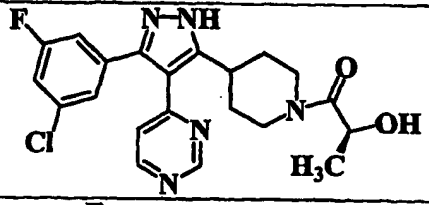
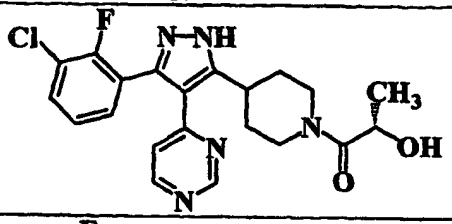
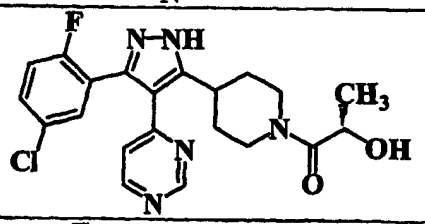
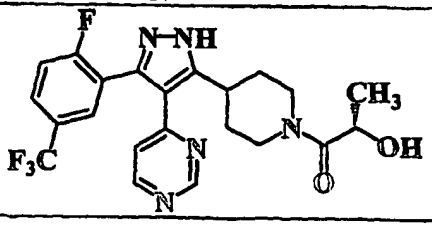
Compound Number	Compound
P-69	
P-70	
P-71	
P-72	
P-73	
P-74	
P-75	

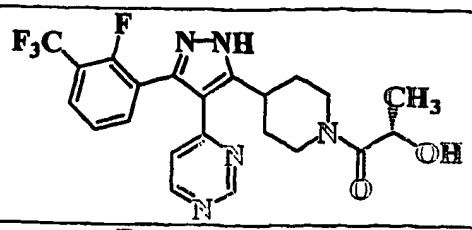
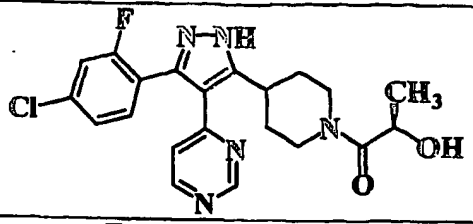
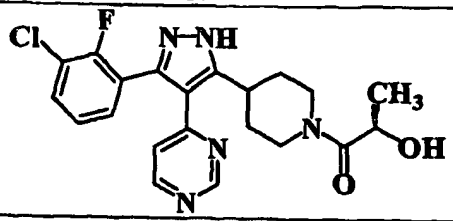
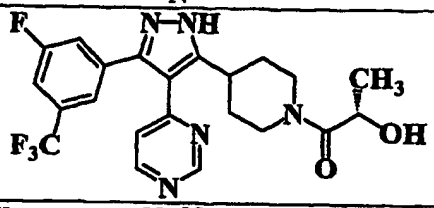
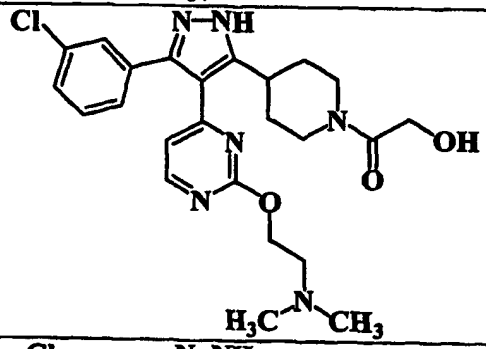
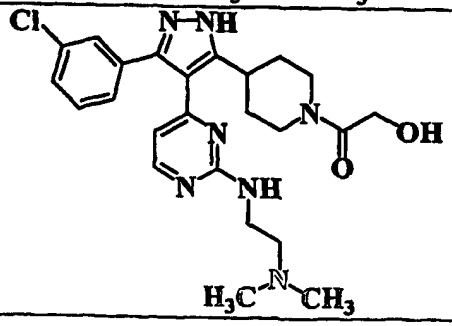
Compound Number	Compound
P-76	
P-77	
P-78	
P-79	
P-80	
P-81	
P-82	

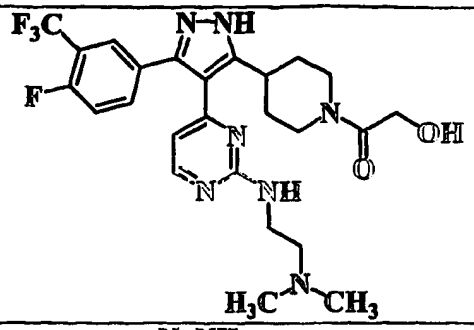
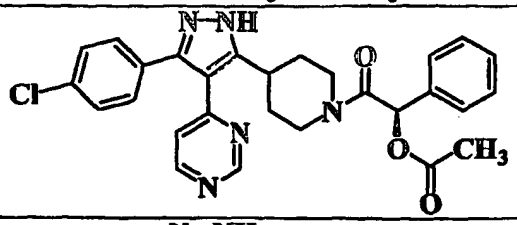
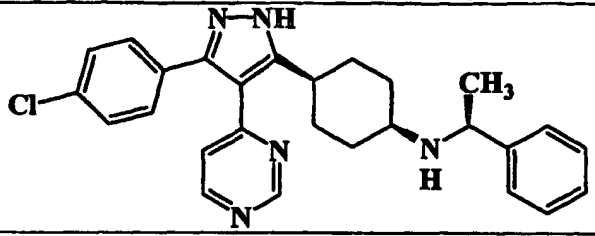
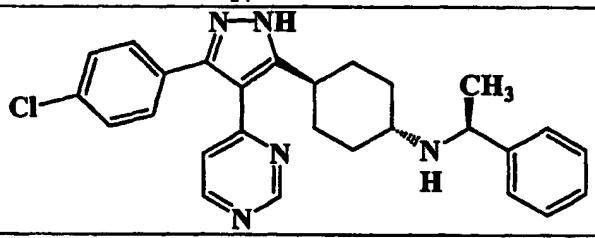
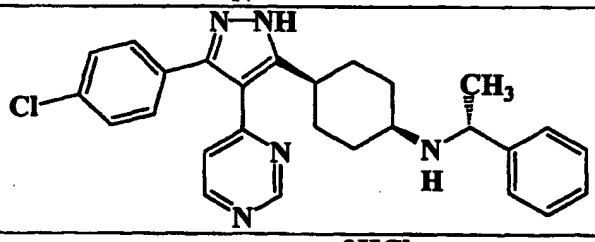
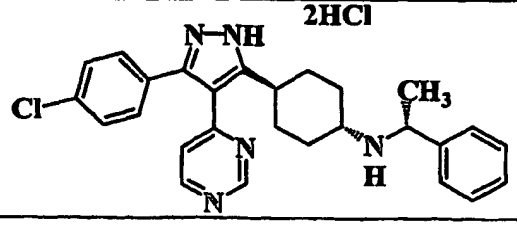
Compound Number	Compound
P-83	
P-84	
P-85	
P-86	
P-87	

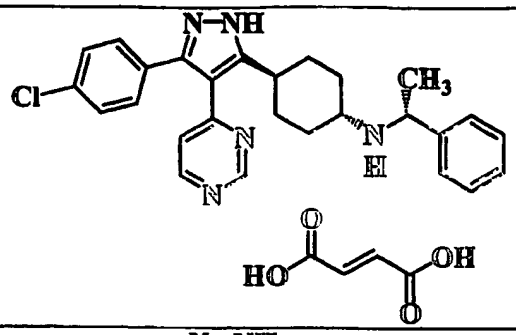
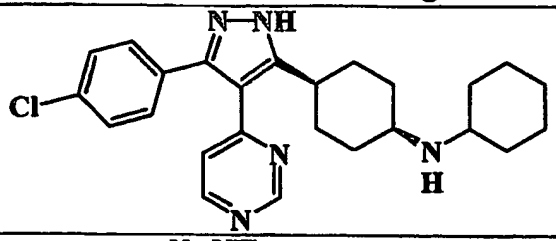
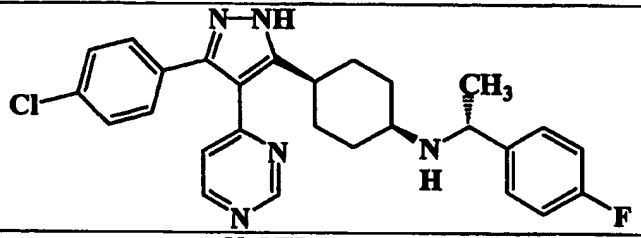
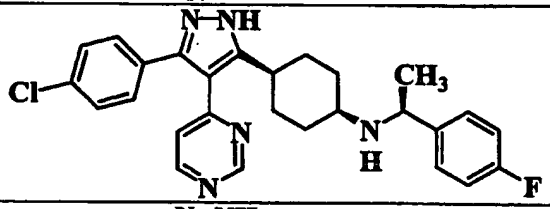
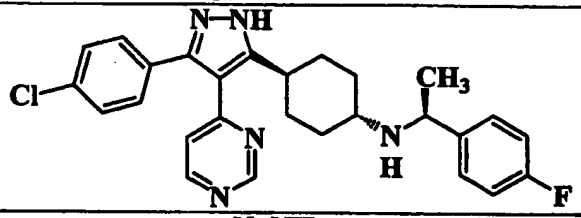
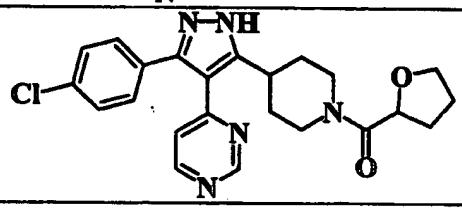
Compound Number	Compound
P-88	
P-89	
P-90	
P-91	
P-92	

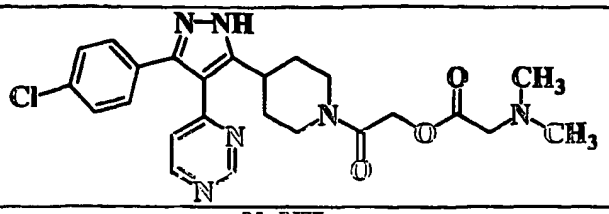
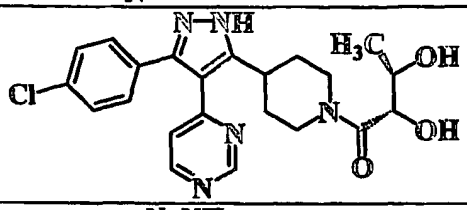
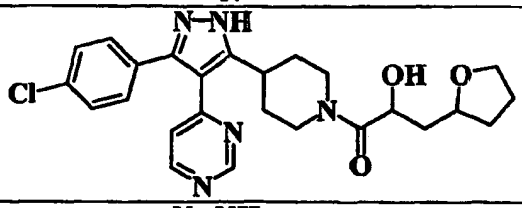
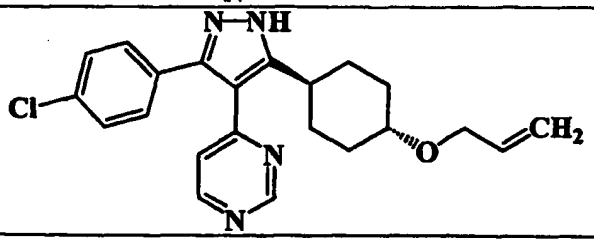
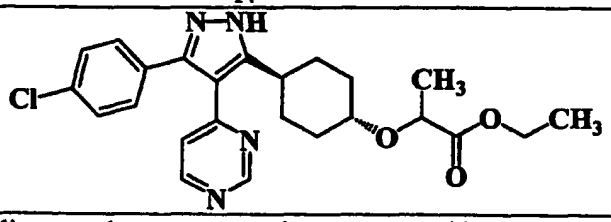
Compound Number	Compound
P-93	
P-94	
P-95	
P-96	
P-97	
P-98	

Compound Number	Compound
P-99	
P-100	
P-101	
P-102	
P-103	
P-104	
P-105	

Compound Number	Compound
P-106	
P-107	
P-108	
P-109	
P-110	
P-111	

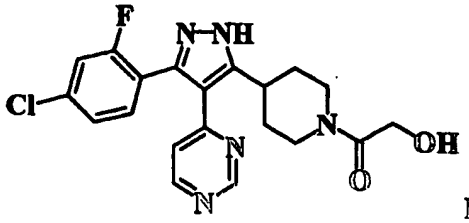
Compound Number	Compound
P-112	
P-113	
P-114	
P-115	
P-116	
P-117	2HCl 

Compound Number	Compound
P-118	
P-119	
P-120	
P-121	
P-122	
P-123	

Compound Number	Compound
P-124	
P-125	
P-126	
P-127	
P-128	

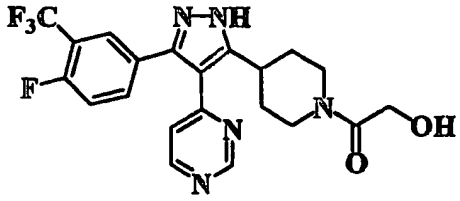
In some preferred embodiments, these compounds are prepared by a process disclosed by Allen et al. in U.S. Patent Application No. 10/254,445; and PCT Application No. PCT/US02/30409 (both of which are cited above incorporated by reference into this patent).

[91] In some embodiments wherein the p38-kinase inhibitor comprises a substituted pyrazole, the p38-kinase inhibitor corresponds in structure to **Formula P-48:**



P-48.

[92] In some embodiments wherein the p38-kinase inhibitor comprises a substituted pyrazole, the p38-kinase inhibitor corresponds in structure to **Formula P-49**:

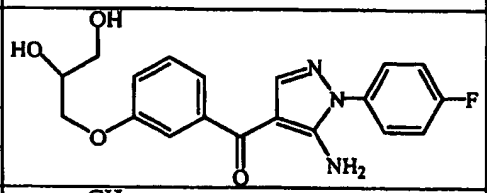
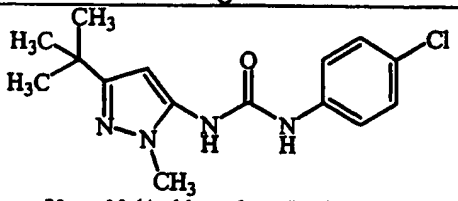


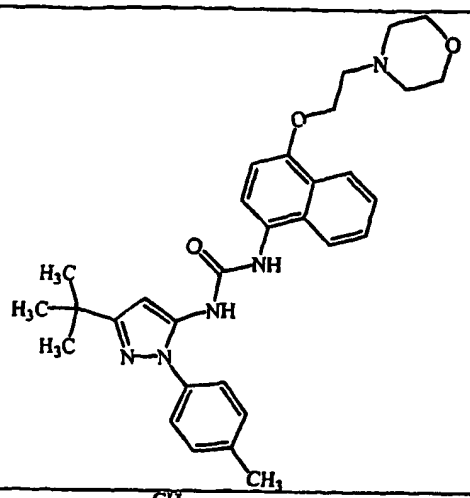
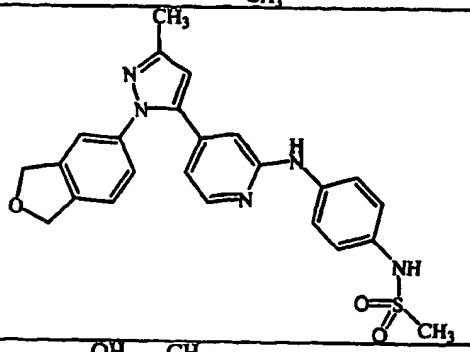
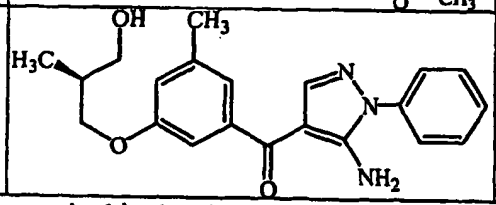
P-49.

[93] In some embodiments, the p38-kinase inhibitor comprises a substituted pyrazole corresponding in structure to an analogue of a compound in **Table 1 or 2** wherein the pyrimidine at the 4-position of the pyrazole has been replaced with a pyridine.

[94] In some embodiments wherein the p38-kinase inhibitor comprises a substituted pyrazole, the p38-kinase inhibitor comprises a compound selected from the group of reported p38-kinase inhibitors in **Table 3**:

Table 3

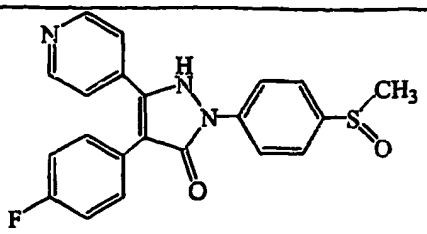
Compound Number	Compound	Compound Identifier	CAS Registry Number	Patent / Literature Reference(s) for Compound
P-129				
P-130	 Urea, N-(4-chlorophenyl)-N'-[3-(1,1-dimethylethyl)-1-methyl-1H-pyrazol-5-yl]-(9CI)		432042-02-9	*Nature Structural Biology*, 9(4), 268-272 (2002); *Journal of Medicinal Chemistry*, 45(14), 2994-3008 (2002).

Compound Number	Compound	Compound Identifier	CAS Registry Number	Patent / Literature Reference(s) for Compound
P-131		BIRB 786		
P-132				WO 02/072571
P-133				

The references cited in the above table generally disclose methods for making the corresponding compounds, and are incorporated by reference into this patent.

[95] In some embodiments, the p38-kinase inhibitor comprises the reported p38-kinase inhibitor shown in **Table 4**:

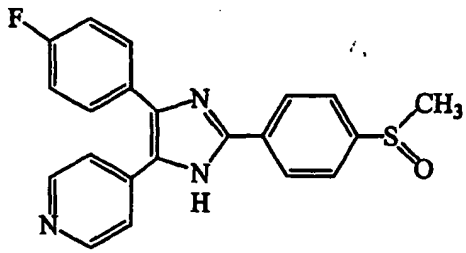
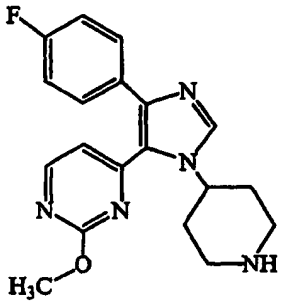
Table 4

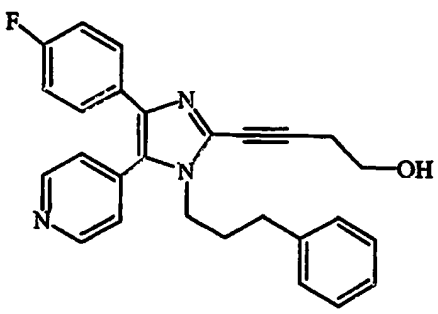
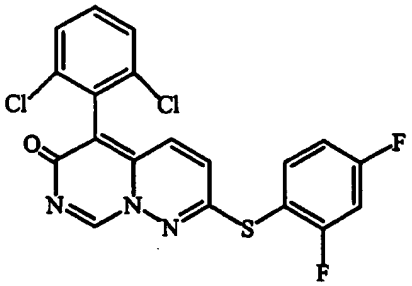
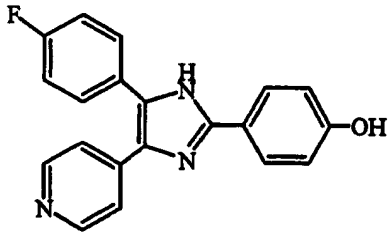
Compound Number	Compound	Compound Identifier	CAS Registry Number	Patent / Literature Reference(s) for Compound
P-134			219138-27-9	*Pharmacol. Ther.* 82: 389-397 (1999); *Bioorganic & Medicinal Chemistry Letters*, 8(19), 2689-2694 (1998).

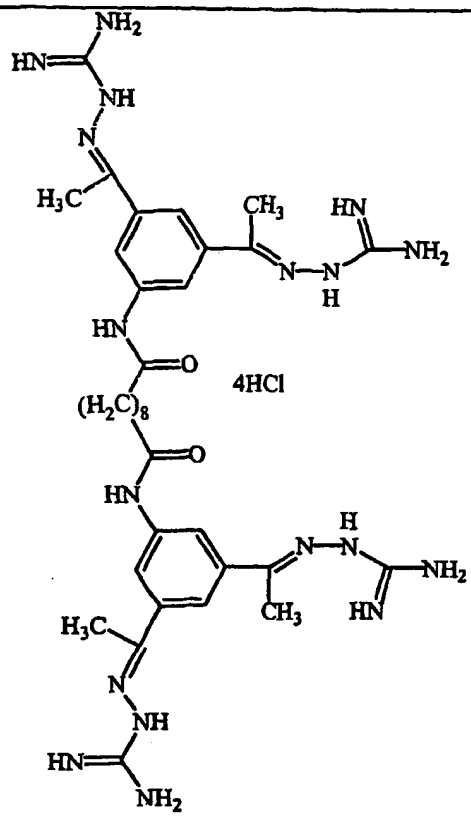
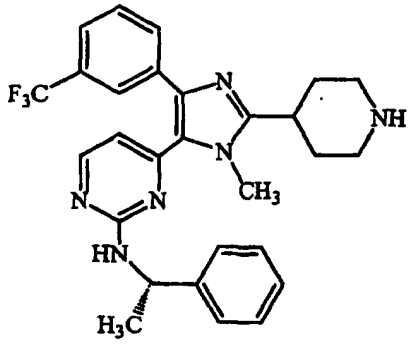
The references cited in the above table generally disclose methods for making the depicted compound, and are incorporated by reference into this patent.

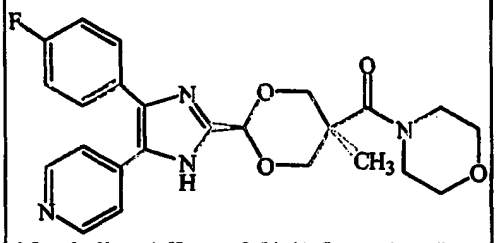
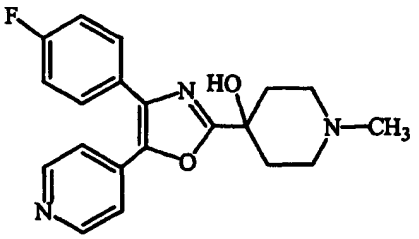
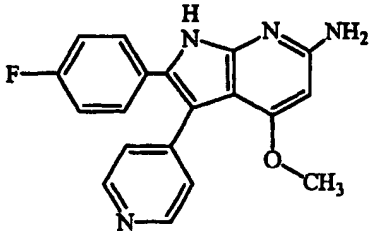
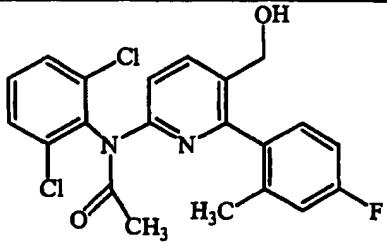
[96] In some embodiments, the p38-kinase inhibitor comprises a reported p38-kinase inhibitor shown in **Table 5**:

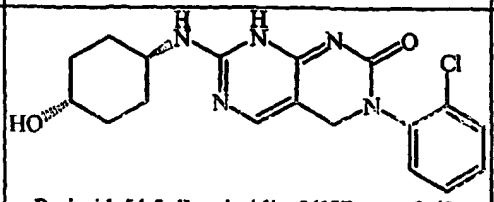
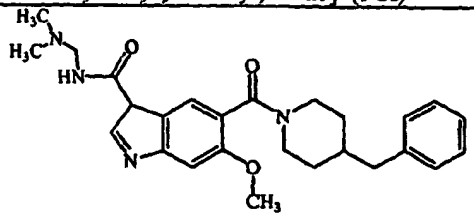
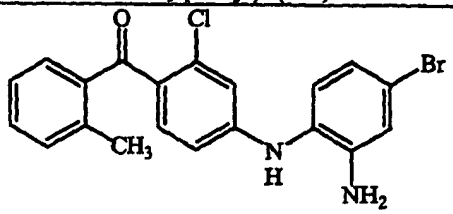
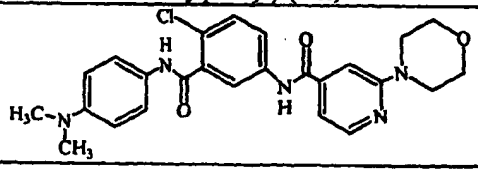
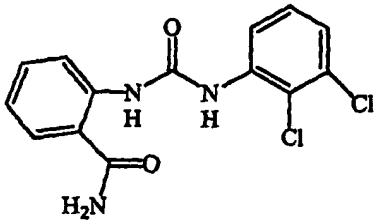
Table 5

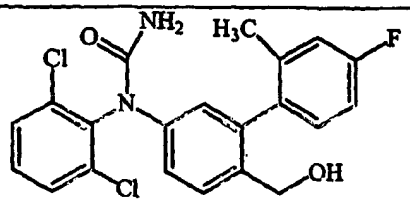
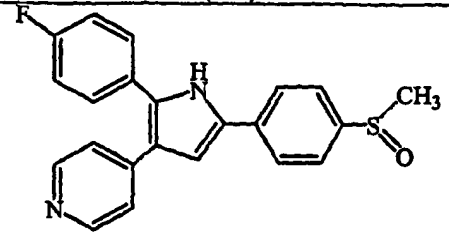
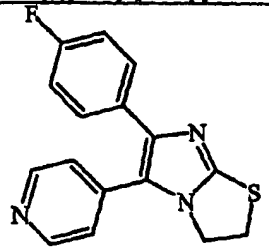
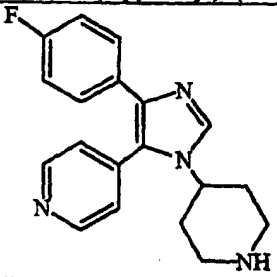
Compound number	Compound	Compound Identifier	CAS Registry Number	Patent / Literature Reference(s) for Compound
P-135	 Pyridine, 4-[5-(4-fluorophenyl)-2-[4-(methylsulfinyl)phenyl]-1H-imidazol-4-yl]-(9CI)	SB203580	152121-47-6	*J. Pharmacol. Exp. Ther.* 279: 1453-1461 (1996) WO 93/14081 WO 95/03297
P-136	 Pyrimidine, 4-[4-(4-fluorophenyl)-1-(4-piperidinyl)-1H-imidazol-5-yl]-2-methoxy-(9CI)	SB242235	193746-75-7	WO 97/25046 US 5,716,955

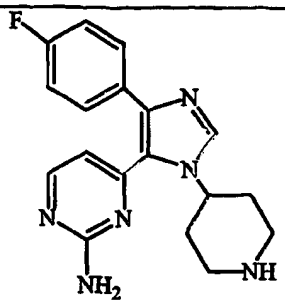
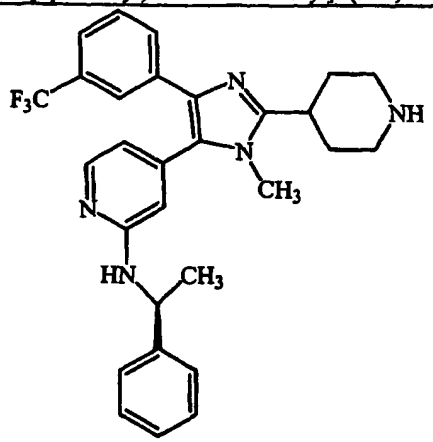
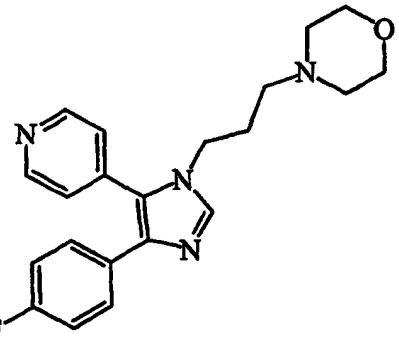
Compound number	Compound	Compound Identifier	CAS Registry Number	Patent / Literature Reference(s) for Compound
P-137	 3-Butyn-1-ol, 4-[4-(4-fluorophenyl)-1-(3-phenylpropyl)-5-(4-pyridinyl)-1*H*-imidazol-2-yl]-(9Cl)	RWJ67657	215303-72-3	WO 98/47892
P-138	 6H-Pyrimido[1,6-b]pyridazin-6-one, 5-(2,6-dichlorophenyl)-2-[(2,4-difluorophenyl)thio]-(9Cl)	VX-745	209410-46-8	WO 98/27098
P-139	 Phenol, 4-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1*H*-imidazol-2-yl]-(9Cl)	SB202190	152121-30-7	WO 93/14081 US 5,656,644 US 5,686,455

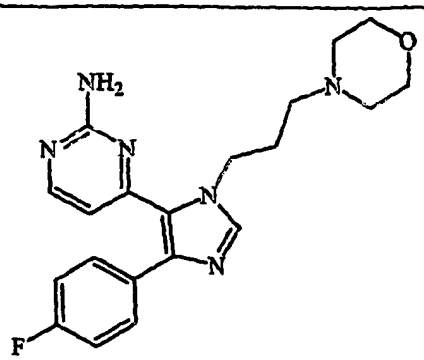
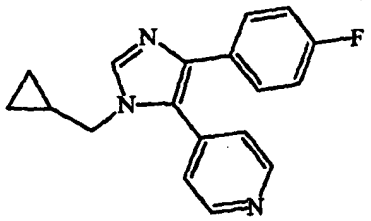
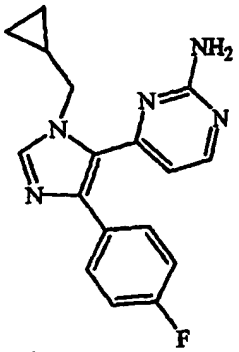
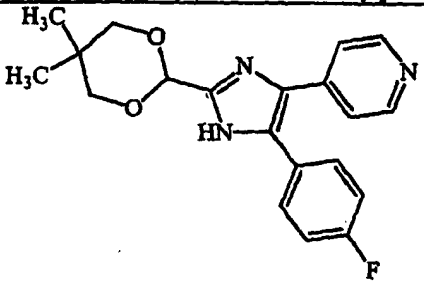
Compound number	Compound	Compound Identifier	CAS Registry Number	Patent / Literature Reference(s) for Compound
P-140	 4HCl decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl], tetrahydrochloride (9CI)	CNI-1493	164301-51-3	WO 9519767 WO 9820868 US 5750573
P-141	 2-Pyrimidinamine, 4-[1-methyl-2-(4-piperidinyl)-4-[3-(trifluoromethyl)phenyl]-1H-imidazol-5-yl]-N-(1-phenylethyl)-, (R)- (9CI)		200801-85-0	*Journal of Medicinal Chemistry* 42(12): 2180-2190 (1999) WO 97/47618

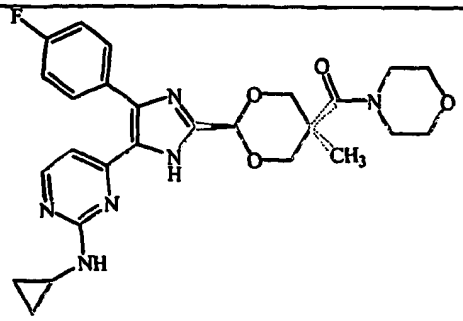
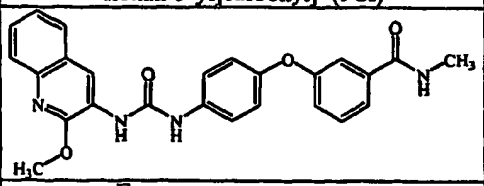
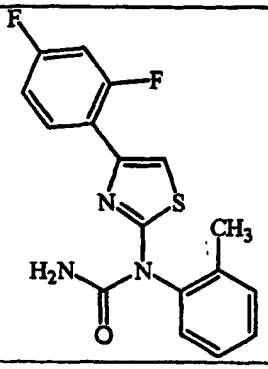
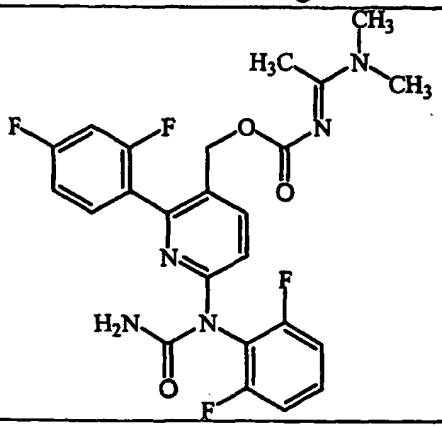
Compound number	Compound	Compound Identifier	CAS Registry Number	Patent / Literature Reference(s) for Compound
P-142	 Morpholine, 4-[[trans-2-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1*H*-imidazol-2-yl]-5-methyl-1,3-dioxan-5-yl]carbonyl]-,monomethanesulfonate (9CI)	RPR200765A	218162-38-0	WO 98/56788
P-143	 4-Piperidinol, 4-[4-(4-fluorophenyl)-5-(4-pyridinyl)-2-oxazolyl]-1-methyl- (9CI)		290357-24-3	*Bioorganic & Medicinal Chemistry Letters* 10(11): 1261-1264 (2000)
P-144	 1*H*-Pyrrolo[2,3-b]pyridin-6-amine, 2-(4-fluorophenyl)-4-methoxy-3-(4-pyridinyl)-(9CI)	RWJ68354	215306-39-1	WO 98/47899 *Tetrahedron Letters* 39(48): 8763-8764 (1998)
P-145	 Urea, N-(2,6-dichlorophenyl)-N-[6-(4-fluoro-2-methylphenyl)-5-(hydroxymethyl)-2-pyridinyl]-(9CI)		250123-27-4	WO99/58502

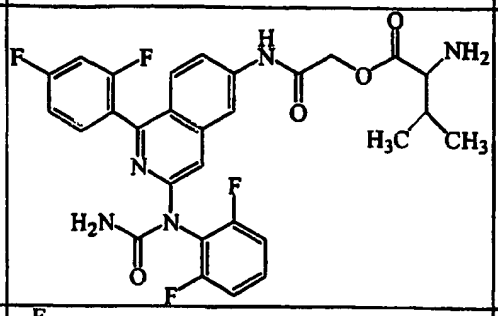
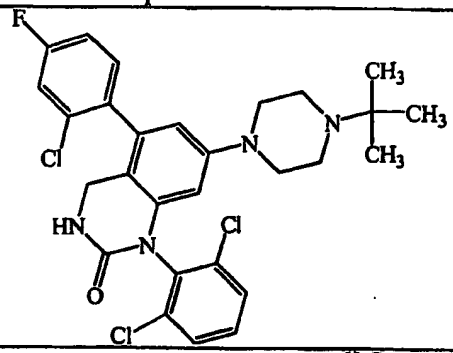
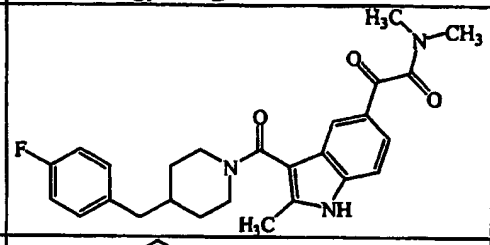
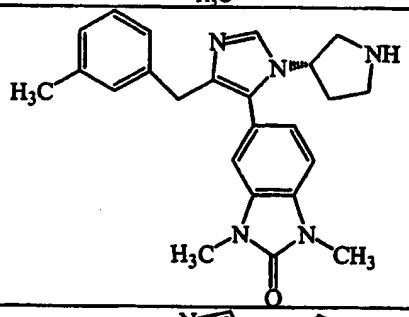
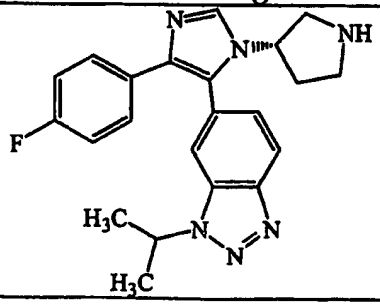
Compound number	Compound	Compound Identifier	CAS Registry Number	Patent / Literature Reference(s) for Compound
P-146	 Pyrimido[4,5-d]pyrimidin-2(1H)-one, 3-(2-chlorophenyl)-3,4-dihydro-7-[(trans-4-hydroxycyclohexyl)amino]- (9CI)		335652-44-3	WO 01/29042
P-147	 Methanone, [4-[(2-amino-4-bromophenyl)amino]-2-chlorophenyl](2-methylphenyl)- (9CI)		321351-00-2	WO 01/12074
P-148	 Methanone, [4-[(2-amino-4-bromophenyl)amino]-2-chlorophenyl](2-methylphenyl)-(9CI)	EO1428	321351-00-2	WO 0105744 WO 0105745 WO 0105746 WO 0105749 WO 0105751
P-149				*Exp. Opin. Ther. Pat.* 11: 1471-1473 (2001)
P-150		Vertex		

Compound number	Compound	Compound Identifier	CAS Registry Number	Patent / Literature Reference(s) for Compound
P-151	 Urea, N-(2,6-dichlorophenyl)-N-[4'-fluoro-6-(hydroxymethyl)-2'-methyl[1,1'-biphenyl]-3-yl]-(9CI)	Vertex	304439-93-8	Sibley et al., Bioorganic & Medicinal Chemistry Letters, 10(13): 2047-2050 (2000).
P-152	 Pyridine, 4-[2-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-1*H*-pyrrol-3-yl]-(9CI)	L-167307	188352-45-6	WO 9705878 WO 9716441 US 5837719 WO 0066124
P-153	 Imidazo[2,1-b]thiazole, 6-(4-fluorophenyl)-2,3-dihydro-5-(4-pyridinyl)- (9CI)	SK&F 86002	72873-74-6	Newton et al., *Drug Metabolism & Disposition*, 17(2): 174-9 (1989). US 4,175,127
P-154	 Pyridine, 4-[4-(4-fluorophenyl)-1-(4-piperidinyl)-1H-imidazol-5-yl]- (9CI)	HEP 689/ SB 235699	180869-32-3	WO 9621452 US 5593992 US 5593991

Compound number	Compound	Compound Identifier	CAS Registry Number	Patent / Literature Reference(s) for Compound
P-155	 2-Pyrimidinamine, 4-[4-(4-fluorophenyl)-1-(4-piperidinyl)-1H-imidazol-5-yl]- (9CI)	SB 220025	165806-53-1	WO 9502591 WO 9621452 US 5593992 WO 9723479
P-156	 2-Pyridinamine, 4-[1-methyl-2-(4-piperidinyl)-4-[3-(trifluoromethyl)phenyl]-1H-imidazol-5-yl]-N-[(1S)-1-phenylethyl]- (9CI)		189442-43-1	WO 9712876 US 5717100 US 6083949
P-157	 Morpholine, 4-[3-[4-(4-fluorophenyl)-5-(4-pyridinyl)-1*H*-imidazol-1-yl]propyl]-(9CI)	SB 210313	165806-09-7	WO 9502591 WO 9621452 US 5593992 US 5670527

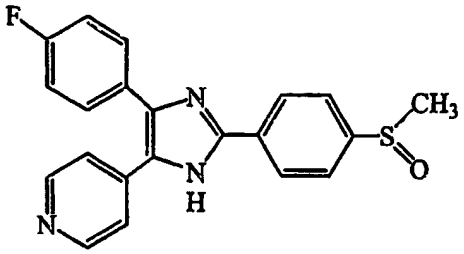
Compound number	Compound	Compound Identifier	CAS Registry Number	Patent / Literature Reference(s) for Compound
P-158	 2-Pyrimidinamine, 4-[4-(4-fluorophenyl)-1-[3-(4-morpholinyl)propyl]-1*H*-imidazol-5-yl]-(9Cl)	SB 216385	165806-48-4	WO 95/02591 WO 96/21452 US 5,593,992
P-159	 pyridine, 4-[1-(cyclopropylmethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl]	SB 216995	165806-34-8	WO 9502591 US 5,593,991 US 5,593,992 US 5670527
P-160	 2-pyrimidinamine, 4-[1-(cyclopropylmethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl]	SB 218655	165806-51-9	WO 9502591 US 5,593,991 US 5,593,992 US 5670527
P-161	 Pyridine, 4-[2-(5,5-dimethyl-1,3-dioxan-2-yl)-5-(4-fluorophenyl)-1*H*-imidazol-4-yl]-(9Cl)	RPR-132331	218145-98-3	WO 9856788

Compound number	Compound	Compound Identifier	CAS Registry Number	Patent / Literature Reference(s) for Compound
P-162	 Morpholine, 4-[[trans-2-[4-[2-(cyclopropylamino)-4-pyrimidinyl]-5-(4-fluorophenyl)-1H-imidazol-2-yl]-5-methyl-1,3-dioxan-5-yl]carbonyl]- (9CI)	RPR-203494	218160-26-0	WO 9856788; Bioorganic & Medicinal Chemistry Letters 11(5), 693-696 (2001)
P-163				
P-164				WO 00/17175
P-165				WO 01/70695 WO 02/14281

Compound number	Compound	Compound Identifier	CAS Registry Number	Patent / Literature Reference(s) for Compound
P-166				WO 02/100405
P-167				WO 02/058695
P-168				WO 02/42292
P-169				
P-170				EP 02-252153

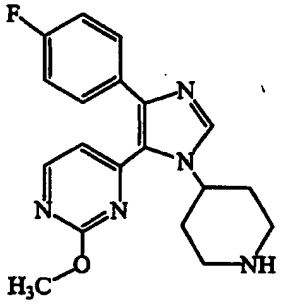
The references cited in the above table generally disclose methods for making the corresponding compounds, and are incorporated by reference into this patent.

[97] In some embodiments, the p38-kinase inhibitor comprises the reported p38-kinase inhibitor corresponding in structure to **Formula P-135**:



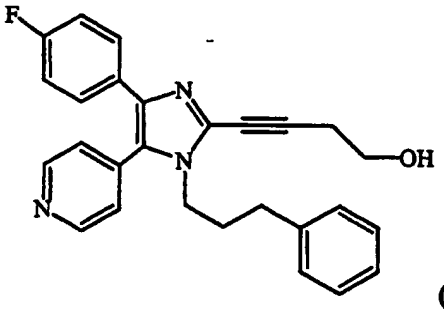
(P-135).

[98] In some embodiments, the p38-kinase inhibitor comprises the reported p38-kinase inhibitor corresponding in structure to **Formula P-136**:



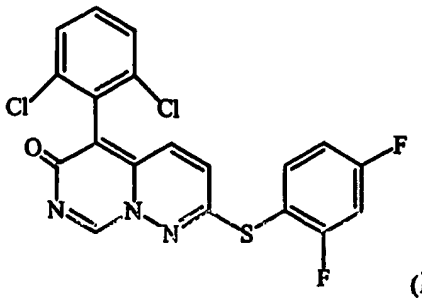
(P-136).

[99] In some embodiments, the p38-kinase inhibitor comprises the reported p38-kinase inhibitor corresponding in structure to **Formula P-137**:



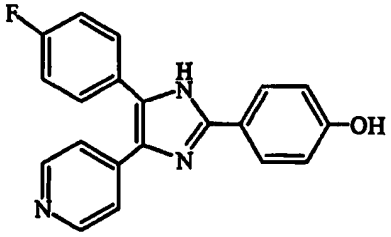
(P-137).

[100] In some embodiments, the p38-kinase inhibitor comprises the reported p38-kinase inhibitor corresponding in structure to **Formula P-138**:



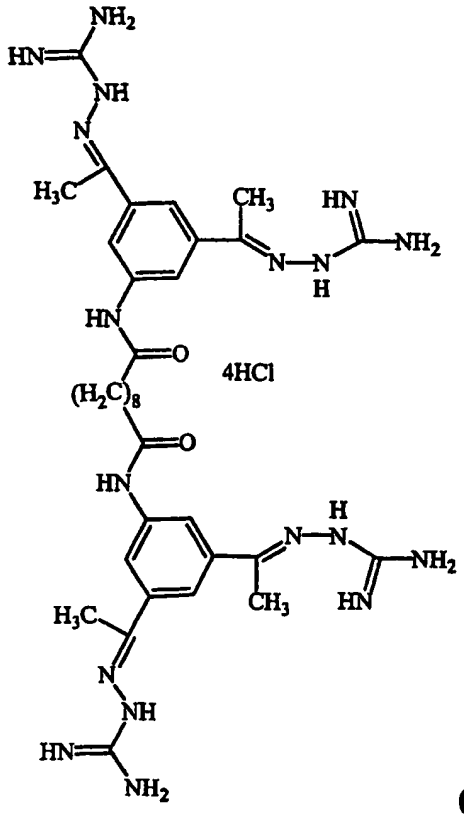
(P-138).

[101] In some embodiments, the p38-kinase inhibitor comprises the reported p38-kinase inhibitor corresponding in structure to **Formula P-139**:



(P-139).

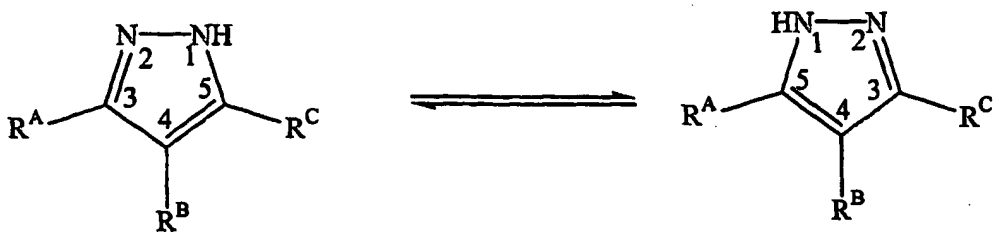
[102] In some embodiments, the p38-kinase inhibitor comprises the reported p38-kinase inhibitor corresponding in structure to **Formula P-140**:



(P-140).

[103] In many preferred embodiments, the p38-kinase inhibitor comprises a substituted imidazole.

[104] Other contemplated p38-kinase inhibitors include diastomers, enantiomers, racemates, salts, conjugate acids, and pro-drugs of the above-described compounds. The present invention further contemplates any tautomeric forms of the above-described compounds. For example, pyrazoles of Formula I and I' are magnetically and structurally equivalent because of the prototropic tautomeric nature of the hydrogen:



[105] The typically preferred mode for this invention is to administer one or more p38-kinase inhibitors in combination with one or more angiotensin-converting-enzyme inhibitors to treat an above-described disease. It should be recognized, however, that this invention also embraces the use of one or more p38-kinase inhibitors (particularly substituted-pyrazole p38-kinase inhibitors, and even more particularly substituted-pyrazole p38-kinase inhibitors described above) alone to treat the above-described diseases.

B. Examples of Angiotensin-Converting-Enzyme Inhibitors

[106] The phrase "angiotensin-converting-enzyme inhibitor" (or "ACE inhibitor") includes an agent or compound, or a combination of two or more agents or compounds, having the ability to block, partially or completely, the enzymatic conversion of the decapeptide form of angiotensin ("angiotensin I") to the vasoconstrictive octapeptide form of angiotensin ("angiotensin II"). Blocking the formation of angiotensin II can affect the regulation of fluid and electrolyte balance, blood pressure, and blood volume by removing the primary actions of angiotensin II. Included in these primary actions of angiotensin II are stimulation of the synthesis and secretion of aldosterone receptor by the adrenal cortex and raising blood pressure by direct constriction of the smooth muscle of the arterioles.

[107] Examples of ACE inhibitors that may be used in the combination therapy of this invention include the following compounds: AB-103, ancovenin, benazeprilat,

BRL-36378, BW-A575C, CGS-13928C, CL-242817, CV-5975, Equaten, EU-4865, EU-4867, EU-5476, foroxymithine, FPL 66564, FR-900456, Hoe-065, I5B2, indolapril, ketomethylureas, KRI-1177, KRI-1230, L-681176, libenzapril, MCD, MDL-27088, MDL-27467A, moveltipril, MS-41, nicotianamine, pentopril, phenacein, pivopril, rentiapril, RG-5975, RG-6134, RG-6207, RGH-0399, ROO-911, RS-10085-197, RS-2039, RS 5139, RS 86127, RU-44403, S-8308, SA-291, spiraprilat, SQ-26900, SQ-28084, SQ-28370, SQ-28940, SQ-31440, Synecor, utibapril, WF-10129, Wy-44221, Wy-44655, Y-23785, Yissum P-0154, zabicipril, Asahi Brewery AB-47, alatriopril, BMS 182657, Asahi Chemical C-111, Asahi Chemical C-112, Dainippon DU-1777, mixanpril, prentyl, zofenoprilat, 1-(-(1-carboxy-6-(4-piperidinyl)hexyl)amino)-1-oxopropyl octahydro-1H-indole-2-carboxylic acid, Bioproject BP1.137, Chiesi CHF 1514, Fisons FPL-66564, idrapril, Marion Merrell Dow MDL-100240, perindoprilat and Servier S-5590, alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, saralasin acetate, temocapril, trandolapril, ceronapril, moexipril, quinaprilat, and spirapril.

[108] A group of ACE inhibitors of particular interest consists of alacepril, benazepril, captopril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, perindopril, quinapril, ramipril, saralasin acetate, temocapril, trandolapril, ceronapril, moexipril, quinaprilat, and spirapril.

[109] In some embodiments, the ACE inhibitor comprises a compound selected from the group consisting of those in **Table 6**:

Table 6

Compound Number	Compound Name	Reference
ACE-1	alacepril	U.S. Patent No. 4,248,883
ACE-2	benazepril	U.S. Patent No. 4,410,520
ACE-3	captopril	U.S. Patent Nos. 4,046,889 & 4,105,776
ACE-4	ceronapril	U.S. Patent No. 4,452,790
ACE-5	delapril	U.S. Patent No. 4,385,051
ACE-6	enalapril	U.S. Patent No. 4,374,829
ACE-7	fosinopril	U.S. Patent No. 4,337,201
ACE-8	imadapril	U.S. Patent No. 4,508,727
ACE-9	lisinopril	U.S. Patent No. 4,555,502

ACE-10	moveltipril	Belgian Patent No. 893,553
ACE-11	perindopril	U.S. Patent No. 4,508,729
ACE-12	quinapril	U.S. Patent No. 4,344,949
ACE-13	ramipril	U.S. Patent No. 4,587,258
ACE-14	spirapril	U.S. Patent No. 4,470,972
ACE-15	temocapril	U.S. Patent No. 4,699,905
ACE-16	trandolapril	U.S. Patent No. 4,933,361

The references cited in the above table generally disclose methods for making the corresponding compounds, and are incorporated by reference into this patent.

[110] In some embodiments, the ACE inhibitor comprises benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, or spirapril.

[111] In some embodiments, the ACE inhibitor comprises benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril, or moexipril.

[112] In some embodiments, the ACE inhibitor comprises enalapril.

C. Definitions

[113] The phrase "treating a condition" means ameliorating, suppressing, eradicating, reducing the severity of, decreasing the frequency of incidence of, preventing, reducing the risk of, and/or delaying the onset of the condition.

[114] The term "combination therapy" means the administration of two or more therapeutic agents to treat a pathological condition. In this specification, the pathological condition generally comprises a cardiovascular condition or a condition associated with a cardiovascular condition. The therapeutic agents of the combination generally may be co-administered in a substantially simultaneous manner, such as, for example, (a) in a single formulation (*e.g.*, a single capsule) having a fixed ratio of active ingredients, or (b) in multiple, separate formulations (*e.g.*, multiple capsules) for each agent. The therapeutic agents of the combination may alternatively (or additionally) be administered at different times. In either case, the chosen treatment regimen preferably provides beneficial effects of the drug combination in treating the condition.

[115] The phrase "therapeutically-effective" qualifies the amount of each therapeutic agent that will achieve the goal of ameliorating, suppressing, eradicating, reducing the severity of, decreasing the frequency of incidence of, preventing, reducing the risk of, and/or delaying the onset of a pathological condition.

[116] The term "pharmaceutically-acceptable" is used adjectivally to mean that the modified noun is appropriate for use in a pharmaceutical product. When it is used, for example, to describe a carrier in a pharmaceutical composition, it characterizes the carrier as being compatible with the other ingredients of the composition and not deleterious to the recipient. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, for example, appropriate alkali metal salts, alkaline earth metal salts, and other physiologically acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc in their usual valences. Preferred organic ions include protonated amines and quaternary ammonium cations, including, in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Exemplary pharmaceutically acceptable acids include, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid, oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

[117] With reference to the use of the words "comprise" or "comprises" or "comprising" in this patent (including the claims), Applicants note that unless the context requires otherwise, those words are used on the basis and clear understanding that they are to be interpreted inclusively, rather than exclusively.

D. Hypothetical Mechanisms of Action in Combination Therapies

[118] Without being held to a specific mechanism of action for the combination therapies described in this patent, Applicants hypothesize that the administration of a p38-kinase inhibitor in combination with, for example, an ACE inhibitor may be particularly effective because of the simultaneous, differential mechanisms of the two distinct classes of drugs. More specifically, Applicants' have observed that p38-kinase activity in the left ventricle of spontaneously-hypertensive-heart-failure ("SHHF") rats receiving a p38-kinase inhibitor was markedly reduced compared to untreated SHHF rats. Applicants observed this reduced p38-kinase activity independent of ACE inhibition. In contrast, Applicants observed little impact on myocardial p38-kinase activity when an ACE

inhibitor alone was administered. These findings indicate a direct link between p38-kinase inhibition in myocardial tissue and the efficacy p38-kinase-inhibitor mono-therapy and p38-kinase-inhibitor/ACE-inhibitor combination therapy. These findings, however, also suggest that the cardio-protective effects of ACE inhibition and p38-kinase inhibition occur, at least in part, via differential mechanisms. Such differential mechanisms, in turn, are believed to generally provide a basis for an improved efficacy of a combination therapy comprising the administration of a p38-kinase inhibitor and an ACE inhibitor over a p38-kinase inhibitor or ACE inhibitor alone.

[119] In addition to the benefits from the differential mechanisms, Applicants also believe that p38-kinase-inhibition therapies and, for example, ACE-inhibition therapies may also share simultaneous, interrelated mechanisms that may make a p38-kinase-inhibition/ACE-inhibition combination therapy particularly effective. This belief is based on, for example, Applicants' investigations of the mechanisms for attenuation of left ventricular remodeling. Specifically, Applicants investigated the impact of p38-kinase inhibition, ACE inhibition, and co-administration therapy on left ventricular matrix metalloprotease ("MMP") activity and expression. Gelatinase activity and matrix metalloproteinase-2 (MMP-2) expression were decreased by p38-kinase inhibition alone, ACE inhibition alone, and co-administration therapy. Thus, for example, modulation of MMP's may represent a common mechanism for attenuation of maladaptive left ventricular remodeling by p38-kinase inhibition and ACE inhibition in heart failure.

[120] Benefits from the combination therapies contemplated in this patent (relative to mono-therapies using a p38-kinase inhibitor or ACE inhibitor alone) may include, for example, greater dosing flexibility; a reduction in the dosages of the p38-kinase inhibitor or cardiovascular therapeutic agent; fewer and/or less-severe side effects (particularly where there is a reduction in dosage); greater therapeutic effect(s); quicker onset of the therapeutic effect(s); and/or longer duration of the therapeutic effect(s).

E. Preferred Dosages and Treatment Regimen

[121] This invention is directed, in part, to a method for preventing or treating a cardiovascular condition, and/or a condition associated with a cardiovascular condition in a subject (particularly a mammal, such as a human, companion animal, farm animal,

laboratory animal, zoo animal, or wild animal) having or disposed to having such a condition(s).

[122] A contemplated combination therapy of this invention comprises dosing a first amount of a p38-kinase inhibitor and a second amount of an ACE inhibitor such that the first and second amounts together form a therapeutically-effective treatment for the targeted condition(s). It should be recognized that the specific dose level and frequency of dosing for the p38-kinase inhibitor and other therapeutic agents will depend on a variety of factors including, for example, the particular combination of agents selected; the activity, efficacy, pharmacokinetic, and toxicology profiles of the particular therapeutic agents used (including such profiles when the agents are used in combination); the age, weight, general health, sex, and diet of the patient; the frequency of administration; the rate of excretion; the condition(s) being treated; the severity of the condition(s) being treated; whether a drug delivery system is used; the form, route, and frequency of administration; and whether other pharmaceutically-active compounds also are being administered. Thus, the dosage regimen actually employed may vary widely, and therefore may deviate from the preferred dosage regimens set forth in this patent.

[123] The total daily dose of each drug generally may be administered to the patient in a single dose, or in proportionate multiple sub-doses. Sub-doses typically are administered from 2 to about 6 times per day, and more typically from 2 to about 4 times per day. Doses may be in an immediate-release form or sustained-release form effective to obtain desired results. It should be recognized that, although the dosing frequency for the therapeutic agents in this invention is typically daily or multiple times per day, this invention also contemplates dosing regimens wherein the preferred period between administration of one or more of the therapeutic agents is greater than 24 hours. In such embodiments, the dosing frequency may be, for example, every 36 hours, every 48 hours, every 72 hours, weekly, or monthly.

[124] In combination therapies comprising a p38-kinase inhibitor and an ACE inhibitor, the administration may comprise administering the p38-kinase inhibitor and the ACE inhibitor in a substantially simultaneous manner using either a single formulation (*e.g.*, a single capsule) having a fixed ratio of the therapeutic agents, or separate formulations (*e.g.*, multiple capsules) that each comprise at least one of the therapeutic agents. Such administration also may comprise administering the p38-kinase inhibitor and

other therapeutic agent at different times in separate formulations. This may include, for example, administering the components of the combination in a sequential manner. Or it may include administering one component multiple times between the administration of another component. Or it may include administering two components at the same time, while also separately administering another portion at least one of those components at a different time as well. Or it may include administering the two components sequentially for a two-step effect. Where the components of the combination are dosed separately, the time period between the dosing of each component may range from a few minutes to several hours or days, and will depend on, for example, the properties of each component (*e.g.*, potency, solubility, bioavailability, half-life, and kinetic profile), as well as the condition of the patient.

[125] The following describes typical dosages and frequencies for p38-kinase inhibitors, and particularly for combinations comprising p38-kinase inhibitors with ACE inhibitors. Further dosage and dosage-frequency optimization (to the extent desirable) may be determined in trials. It should be recognized that multiple doses per day typically may be used to increase the total daily dose, if desired.

[126] The preferred total daily dose of the p38-kinase inhibitor is typically from about 0.01 to about 100 mg/kg, more typically from about 0.1 to about 50 mg/kg, and even more typically from about 0.5 to about 30 mg/kg (*i.e.*, mg p38-kinase inhibitor per kg body weight). A p38-kinase inhibitor typically is administered as a single daily dose, or split into from 2 to about 4 sub-doses per day.

[127] The dosage level for an ACE inhibitor generally will depend on the particular potency of the particular ACE inhibitor used (in addition to, for example, the factors outlined above for dosage levels in general).

[128] In some embodiments, for example, the ACE inhibitor comprises benazepril, and the preferred dosage range is from about 10 to about 80 mg/day for a human of average weight (*i.e.*, 70 kg). In other embodiments, the preferred dosage range is from about 10 to about 40 mg/day. Benazepril typically is administered as a single daily dose, or split into 2 sub-doses per day.

[129] In some embodiments, the ACE inhibitor comprises captopril, and the preferred dosage range is from about 12 to about 150 mg/day. This dosage typically is split into 2 or 3 (more typically 2) sub-doses per day.

[130] In some embodiments, the ACE inhibitor comprises cilazapril, and the preferred dosage range is from about 2.5 to about 5 mg/day. Cilazapril typically is administered as a single daily dose, or split into 2 sub-doses per day.

[131] In some embodiments, the ACE inhibitor comprises enalapril, and the preferred dosage range is from about 2.5 to about 40 mg/day. Enalapril typically is administered as a single daily dose, or split into 2 sub-doses per day.

[132] In some embodiments, the ACE inhibitor comprises fosinopril, and the preferred dosage range is from about 2 to about 80 mg/day. In other embodiments, the preferred dosage range is from about 10 to about 40 mg/day. Fosinopril typically is administered as a single daily dose, or split into 2 sub-doses per day.

[133] In some embodiments, the ACE inhibitor comprises lisinopril, and the preferred dosage range is from about 1 to about 80 mg/day. In other embodiments, the preferred dosage range is from about 5 to about 40 mg/day. Lisinopril typically is administered as a single daily dose, or split into 2 sub-doses per day.

[134] In some embodiments, the ACE inhibitor comprises perindopril, and the preferred dosage range is from about 1 to about 25 mg/day. In other embodiments, the preferred dosage range is from about 1 to about 16 mg/day. Perindopril typically is administered as a single daily dose, or split into 2 sub-doses per day.

[135] In some embodiments, the ACE inhibitor comprises quinapril, and the preferred dosage range is from about 1 to about 250 mg/day. In other embodiments, the preferred dosage range is from about 5 to about 80 mg/day. Quinapril typically is administered as a single daily dose, or split into 2 sub-doses per day.

[136] In some embodiments, the ACE inhibitor comprises ramipril, and the preferred dosage range is from about 0.25 to about 20 mg/day. In other embodiments, the preferred dosage range is from about 12.5 to about 20 mg/day. Ramipril typically is administered as a single daily dose, or split into 2 sub-doses per day.

[137] In some embodiments, the ACE inhibitor comprises spirapril, and the preferred dosage range is from about 12.5 to about 50 mg/day. Spirapril typically is administered as a single daily dose, or split into multiple sub-doses per day.

[138] In some embodiments, the ACE inhibitor comprises trandolapril, and the preferred dosage range is from about 0.25 to about 25 mg/day. Trandolapril typically is administered as a single daily dose, or split into multiple sub-doses per day.

[139] In some embodiments, the ACE inhibitor comprises moexipril, and the preferred dosage range is from about 1 to about 100 mg/day. Moexipril typically is administered as a single daily dose, or split into multiple sub-doses per day.

[140] It should be recognized that it is often preferred to start dosing at an intermediate level, and then titrate up or down, depending on observed efficacy and side-effects.

[141] It also should be recognized that some ACE inhibitors (*e.g.*, benazepril, captopril, enalapril, lisinopril, perindopril, quinapril, and ramipril) are excreted by the kidney and therefore may require a lesser dosage in the presence of a renal impairment (*e.g.*, serum creatine $\geq 221/\mu mol/L$ ≥ 2.5 mg/dl).

[142] It should be recognized that it is often preferred to start dosing the therapeutic agents of the combination at an intermediate levels (particularly an intermediate levels falling within the above-described preferred dosage ranges), and then titrate up or down, depending on observed efficacy and side-effects. In many embodiments, treatment is continued as necessary over a period of several weeks to several months or years until the condition(s) has been controlled or eliminated. Patients undergoing treatment with the p38-kinase inhibitors (and combinations comprising p38-kinase inhibitors) disclosed herein can be routinely monitored by a wide variety of methods known in the art for determining the effectiveness of a treatment for the particular condition being treated. This may include, for example, blood pressure, echocardiography; MRI; monitoring C-reactive protein, brain natriuretic peptides ("BNP"), fibrinogen levels, and pro-inflammatory molecule (*e.g.*, TNF-α, MMP-2, MMP-3, MMP-13, etc.) levels in the bloodstream; and, for kidney-related diseases, it also may include, for example, monitoring the urea appearance rate ("UAR"). Continuous analysis of such data permits modification of the treatment regimen during therapy so that optimal effective amounts of each type of therapeutic agent are administered at any time, and so that the duration of treatment can be determined as well. In this way, the treatment regimen/dosing schedule can be rationally modified over the course of therapy so that the lowest amount of each therapeutic agent that together exhibit satisfactory effectiveness is administered, and so that administration is continued only so long as is necessary to successfully treat the condition.

E-1A. Prophylactic Dosing

[143] The combinations of this invention may be administered prophylactically, before a diagnosis of a cardiovascular condition (or associated condition), and to continue administration of the combination during the period of time the subject is susceptible to the condition. Individuals with no remarkable clinical presentation, but that are nonetheless susceptible to pathologic effects, therefore can be placed on a prophylactic dose of the combination. Such prophylactic doses may, but need not, be lower than the doses used to treat the specific pathogenic effect of interest.

E-1B. Cardiovascular Pathology Dosing

[144] In some embodiments of this invention, cardiac pathologies are identified, and an effective dosing and frequency determined, based on blood concentrations of natriuretic peptides. Natriuretic peptides are a group of structurally similar, but genetically distinct, peptides that have diverse actions in cardiovascular, renal, and endocrine homeostasis. Atrial natriuretic peptide ("ANP") and brain natriuretic peptide ("BNP") are of myocardial cell origin and C-type natriuretic peptide ("CNP") is of endothelial origin. ANP and BNP bind to the natriuretic peptide-A receptor ("NPR-A"), which, via 3',5'-cyclic guanosine monophosphate (cGMP), mediates natriuresis, vasodilation, renin inhibition, antimitogenesis, and lusitropic properties. Elevated natriuretic peptide levels in the blood, particularly blood BNP levels, generally are observed in subjects under conditions of blood volume expansion and after vascular injury such as acute myocardial infarction and remain elevated for an extended period of time after the infarction. (Uusimaa et al.: *Int. J. Cardiol,* vol 69, pp. 5-14 (1999). A decrease in natriuretic peptide level relative to the baseline level measured before administration of a combination of this invention indicates a decrease in the pathologic effect of the combination, and, therefore, provides a correlation with inhibition of the pathologic effect. Blood levels of the desired natriuretic peptide level therefore can be compared against the corresponding baseline level before administration of the combination to determine efficacy of the present method in treating the pathologic effect. Based on such natriuretic peptide level measurements, dosing of the combination can be adjusted to reduce the cardiovascular pathologic effect. Cardiac pathologies also can be identified, and the appropriate dosing determined, based on circulating and urinary cGMP Levels. An

increased plasma level of cGMP parallels a fall in mean arterial pressure. Increased urinary excretion of cGMP is correlated with the natriuresis.

[145] In some embodiments, a combination of this invention is administered at a dosage and frequency effective to cause a statistically-significant decrease in tissue or circulating C-reactive protein (CRP) levels.

[146] In some embodiments, a combination of this invention is administered at a dosage and frequency effective to cause a statistically-significant decrease in circulating pro-inflammatory molecule (*e.g.*, TNF-α, MMP-2, MMP-9, and/or MMP-13) levels.

[147] In some embodiments a combination of this invention is administered at a dosage and frequency effective to cause a statistically-significant decrease in circulating fibrinogen levels.

[148] In some embodiments, a combination of this invention is administered to a patient having an ejection fraction of less than about 45%, particularly less than about 40%, and even more particularly less than about 30%. In such embodiments, the combination preferably is administered at a dosage and frequency effective to cause a statistically-significant increase (or preserve, or at least partially preserve) left ventricular ejection fraction.

[149] In some embodiments, a combination of this invention is administered at a dosage and frequency effective to cause a statistically-significant increase (or preserve, or at least partially preserve) stroke volume.

[150] In some embodiments, a combination of this invention is administered at a dosage and frequency effective to cause a statistically-significant decrease in left ventricular end systolic area, end diastolic area, end systolic volume, or end diastolic volume.

[151] In some embodiments, a combination of this invention is administered at a dosage and frequency effective to cause a statistically-significant decrease in left ventricular mass.

[152] In some embodiments, a combination of this invention is administered at a dosage and frequency effective to cause a statistically-significant decrease in interstitial collagen fraction in the heart (which can be monitored by, for example, measuring collagen markers or measuring the stiffness of the heart using, for example, an echocardiogram).

[153] In some embodiments, a combination of this invention is administered based on the presence of myocardial infarction or heart failure or left ventricular hypertrophy. Left ventricular hypertrophy can be identified by echo-cardiogram or magnetic resonance imaging and used to monitor the progress of the treatment and appropriateness of the dosing.

E-1C. Hypertension Dosing

[154] For the treatment of hypertension, the subject is typically first identified as normotensive, borderline hypertensive, or hypertensive based on blood pressure determinations. For humans, in particular, such a determination may be achieved using a seated cuff mercury sphygmomanometer. Individuals may be deemed normotensive when systolic blood pressure and diastolic blood pressure are less than about 125 mm Hg and less than about 80 mm Hg, respectively; borderline hypertensive when systolic blood pressure and diastolic blood pressure are in the range of from about 125 to about 140 mm Hg and from about 80 to about 90 mm Hg, respectively; and hypertensive when systolic blood pressure and diastolic blood pressure are greater than about 140 mm Hg and 90 mm Hg, respectively. As the severity of the hypertensive condition increases, the preferred dose of at least one component of the combination typically increases. Based on post-administration blood pressure measurement, the doses of the components of the combination may be titrated. After an initial evaluation of the subject's response to the treatment, the doses may be increased or decreased accordingly to achieve the desired blood pressure lowering effect.

E-1D. Renal Pathology Dosing

[155] Dosing and frequency to treat pathologies of renal function can be determined and adjusted based on, for example, measurement of proteinuria, microalbuminuria, decreased glomerular filtration rate (GFR), or decreased creatinine clearance. Proteinuria is identified by the presence of greater than about 0.3 g of urinary protein in a 24 hour urine collection. Microalbuminuria is identified by an increase in assayable urinary albumin. Based upon such measurements, dosing of the dosing and frequency of a combination of this invention can be adjusted to ameliorate a renal

pathologic effect.

E-1E. Neuropathy Pathology Dosing

[156] Neuropathy, especially peripheral neuropathy, can be identified by, and dosing and frequency adjustments based on, neurologic exam of sensory deficit or sensory motor ability.

E-1F. Retinopathy Pathology Dosing

[157] Retinopathy can be identified by, and dosing and frequency adjustments based on, opthamologic exam.

E-2. Example Combinations Comprising a p38-Kinase Inhibitors With an ACE Inhibitor

[158] **Table 7** illustrates examples of some of the combinations of the present invention wherein the combination comprises a first amount of a substituted-pyrazole p38-kinase inhibitor and a second amount of an ACE inhibitor:

Table 7

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
1	P-1	alacepril
2	P-1	benazepril
3	P-1	captopril
4	P-1	ceronapril
5	P-1	cilazapril
6	P-1	delapril
7	P-1	enalapril
8	P-1	enalaprilat
9	P-1	fosinopril
10	P-1	fosinoprilat
11	P-1	imadapril
12	P-1	lisinopril
13	P-1	moexipril
14	P-1	moveltipril
15	P-1	perindopril
16	P-1	quinapril
17	P-1	quinaprilat
18	P-1	ramipril
19	P-1	saralasin acetate

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
20	P-1	spirapril
21	P-1	temocapril
22	P-1	trandolapril
23	P-15	alacepril
24	P-15	benazepril
25	P-15	captopril
26	P-15	ceronapril
27	P-15	cilazapril
28	P-15	delapril
29	P-15	enalapril
30	P-15	enalaprilat
31	P-15	fosinopril
32	P-15	fosinoprilat
33	P-15	imadapril
34	P-15	lisinopril
35	P-15	moexipril
36	P-15	moveltipril
37	P-15	perindopril
38	P-15	quinapril
39	P-15	quinaprilat
40	P-15	ramipril
41	P-15	saralasin acetate
42	P-15	spirapril
43	P-15	temocapril
44	P-15	trandolapril
45	P-18	alacepril
46	P-18	benazepril
47	P-18	captopril
48	P-18	ceronapril
49	P-18	cilazapril
50	P-18	delapril
51	P-18	enalapril
52	P-18	enalaprilat
53	P-18	fosinopril
54	P-18	fosinoprilat
55	P-18	imadapril
56	P-18	lisinopril
57	P-18	moexipril
58	P-18	moveltipril
59	P-18	perindopril
60	P-18	quinapril
61	P-18	quinaprilat
62	P-18	ramipril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
63	P-18	saralasin acetate
64	P-18	spirapril
65	P-18	temocapril
66	P-18	trandolapril
67	P-21	alacepril
68	P-21	benazepril
69	P-21	captopril
70	P-21	ceronapril
71	P-21	cilazapril
72	P-21	delapril
73	P-21	enalapril
74	P-21	enalaprilat
75	P-21	fosinopril
76	P-21	fosinoprilat
77	P-21	imadapril
78	P-21	lisinopril
79	P-21	moexipril
80	P-21	moveltipril
81	P-21	perindopril
82	P-21	quinapril
83	P-21	quinaprilat
84	P-21	ramipril
85	P-21	saralasin acetate
86	P-21	spirapril
87	P-21	temocapril
88	P-21	trandolapril
89	P-48	alacepril
90	P-48	benazepril
91	P-48	captopril
92	P-48	ceronapril
93	P-48	cilazapril
94	P-48	delapril
95	P-48	enalapril
96	P-48	enalaprilat
97	P-48	fosinopril
98	P-48	fosinoprilat
99	P-48	imadapril
100	P-48	lisinopril
101	P-48	moexipril
102	P-48	moveltipril
103	P-48	perindopril
104	P-48	quinapril
105	P-48	quinaprilat

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
106	P-48	ramipril
107	P-48	saralasin acetate
108	P-48	spirapril
109	P-48	temocapril
110	P-48	trandolapril
111	P-49	alacepril
112	P-49	benazepril
113	P-49	captopril
114	P-49	ceronapril
115	P-49	cilazapril
116	P-49	delapril
117	P-49	enalapril
118	P-49	enalaprilat
119	P-49	fosinopril
120	P-49	fosinoprilat
121	P-49	imadapril
122	P-49	lisinopril
123	P-49	moexipril
124	P-49	moveltipril
125	P-49	perindopril
126	P-49	quinapril
127	P-49	quinaprilat
128	P-49	ramipril
129	P-49	saralasin acetate
130	P-49	spirapril
131	P-49	temocapril
132	P-49	trandolapril

The "P" numbers identifying the p38-kinase inhibitors in **Table 7** correspond to the compound numbers in the tables above. The same is true for the remaining combination tables that follow.

[159] **Table 8** illustrates examples of some of the combinations of the present invention wherein the combination comprises a first amount of a reported substituted-pyrazole p38-kinase inhibitor and a second amount of an ACE inhibitor:

Table 8

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
133	P-129	alacepril
134	P-129	benazepril
135	P-129	captopril
136	P-129	ceronapril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
137	P-129	cilazapril
138	P-129	delapril
139	P-129	enalapril
140	P-129	enalaprilat
141	P-129	fosinopril
142	P-129	fosinoprilat
143	P-129	imadapril
144	P-129	lisinopril
145	P-129	moexipril
146	P-129	moveltipril
147	P-129	perindopril
148	P-129	quinapril
149	P-129	quinaprilat
150	P-129	ramipril
151	P-129	saralasin acetate
152	P-129	spirapril
153	P-129	temocapril
154	P-129	trandolapril
155	P-130	alacepril
156	P-130	benazepril
157	P-130	captopril
158	P-130	ceronapril
159	P-130	cilazapril
160	P-130	delapril
161	P-130	enalapril
162	P-130	enalaprilat
163	P-130	fosinopril
164	P-130	fosinoprilat
165	P-130	imadapril
166	P-130	lisinopril
167	P-130	moexipril
168	P-130	moveltipril
169	P-130	perindopril
170	P-130	quinapril
171	P-130	quinaprilat
172	P-130	ramipril
173	P-130	saralasin acetate
174	P-130	spirapril
175	P-130	temocapril
176	P-130	trandolapril
177	P-131	alacepril
178	P-131	benazepril
179	P-131	captopril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
180	P-131	ceronapril
181	P-131	cilazapril
182	P-131	delapril
183	P-131	enalapril
184	P-131	enalaprilat
185	P-131	fosinopril
186	P-131	fosinoprilat
187	P-131	imadapril
188	P-131	lisinopril
189	P-131	moexipril
190	P-131	moveltipril
191	P-131	perindopril
192	P-131	quinapril
193	P-131	quinaprilat
194	P-131	ramipril
195	P-131	saralasin acetate
196	P-131	spirapril
197	P-131	temocapril
198	P-131	trandolapril
199	P-132	alacepril
200	P-132	benazepril
201	P-132	captopril
202	P-132	ceronapril
203	P-132	cilazapril
204	P-132	delapril
205	P-132	enalapril
206	P-132	enalaprilat
207	P-132	fosinopril
208	P-132	fosinoprilat
209	P-132	imadapril
210	P-132	lisinopril
211	P-132	moexipril
212	P-132	moveltipril
213	P-132	perindopril
214	P-132	quinapril
215	P-132	quinaprilat
216	P-132	ramipril
217	P-132	saralasin acetate
218	P-132	spirapril
219	P-132	temocapril
220	P-132	trandolapril
221	P-133	alacepril
222	P-133	benazepril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
223	P-133	captopril
224	P-133	ceronapril
225	P-133	cilazapril
226	P-133	delapril
227	P-133	enalapril
228	P-133	enalaprilat
229	P-133	fosinopril
230	P-133	fosinoprilat
231	P-133	imadapril
232	P-133	lisinopril
233	P-133	moexipril
234	P-133	moveltipril
235	P-133	perindopril
236	P-133	quinapril
237	P-133	quinaprilat
238	P-133	ramipril
239	P-133	saralasin acetate
240	P-133	spirapril
241	P-133	temocapril
242	P-133	trandolapril

[160] **Table 9** illustrates additional examples of some of the combinations of the present invention wherein the combination comprises a first amount of a reported p38-kinase inhibitor and a second amount of an ACE inhibitor:

Table 9

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
243	P-134	alacepril
244	P-134	benazepril
245	P-134	captopril
246	P-134	ceronapril
247	P-134	cilazapril
248	P-134	delapril
249	P-134	enalapril
250	P-134	enalaprilat
251	P-134	fosinopril
252	P-134	fosinoprilat
253	P-134	imadapril
254	P-134	lisinopril
255	P-134	moexipril
256	P-134	moveltipril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
257	P-134	perindopril
258	P-134	quinapril
259	P-134	quinaprilat
260	P-134	ramipril
261	P-134	saralasin acetate
262	P-134	spirapril
263	P-134	temocapril
264	P-134	trandolapril

[161] **Table 10** illustrates additional examples of some of the combinations of the present invention wherein the combination comprises a first amount of a reported p38-kinase inhibitor and a second amount of an ACE inhibitor:

Table 10

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
265	P-135	alacepril
266	P-135	benazepril
267	P-135	captopril
268	P-135	ceronapril
269	P-135	cilazapril
270	P-135	delapril
271	P-135	enalapril
272	P-135	enalaprilat
273	P-135	fosinopril
274	P-135	fosinoprilat
275	P-135	imadapril
276	P-135	lisinopril
277	P-135	moexipril
278	P-135	moveltipril
279	P-135	perindopril
280	P-135	quinapril
281	P-135	quinaprilat
282	P-135	ramipril
283	P-135	saralasin acetate
284	P-135	spirapril
285	P-135	temocapril
286	P-135	trandolapril
287	P-136	alacepril
288	P-136	benazepril
289	P-136	captopril
290	P-136	ceronapril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
291	P-136	cilazapril
292	P-136	delapril
293	P-136	enalapril
294	P-136	enalaprilat
295	P-136	fosinopril
296	P-136	fosinoprilat
297	P-136	imadapril
298	P-136	lisinopril
299	P-136	moexipril
300	P-136	moveltipril
301	P-136	perindopril
302	P-136	quinapril
303	P-136	quinaprilat
304	P-136	ramipril
305	P-136	saralasin acetate
306	P-136	spirapril
307	P-136	temocapril
308	P-136	trandolapril
309	P-137	alacepril
310	P-137	benazepril
311	P-137	captopril
312	P-137	ceronapril
313	P-137	cilazapril
314	P-137	delapril
315	P-137	enalapril
316	P-137	enalaprilat
317	P-137	fosinopril
318	P-137	fosinoprilat
319	P-137	imadapril
320	P-137	lisinopril
321	P-137	moexipril
322	P-137	moveltipril
323	P-137	perindopril
324	P-137	quinapril
325	P-137	quinaprilat
326	P-137	ramipril
327	P-137	saralasin acetate
328	P-137	spirapril
329	P-137	temocapril
330	P-137	trandolapril
331	P-138	alacepril
332	P-138	benazepril
333	P-138	captopril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
334	P-138	ceronapril
335	P-138	cilazapril
336	P-138	delapril
337	P-138	enalapril
338	P-138	enalaprilat
339	P-138	fosinopril
340	P-138	fosinoprilat
341	P-138	imadapril
342	P-138	lisinopril
343	P-138	moexipril
344	P-138	moveltipril
345	P-138	perindopril
346	P-138	quinapril
347	P-138	quinaprilat
348	P-138	ramipril
349	P-138	saralasin acetate
350	P-138	spirapril
351	P-138	temocapril
352	P-138	trandolapril
353	P-139	alacepril
354	P-139	benazepril
355	P-139	captopril
356	P-139	ceronapril
357	P-139	cilazapril
358	P-139	delapril
359	P-139	enalapril
360	P-139	enalaprilat
361	P-139	fosinopril
362	P-139	fosinoprilat
363	P-139	imadapril
364	P-139	lisinopril
365	P-139	moexipril
366	P-139	moveltipril
367	P-139	perindopril
368	P-139	quinapril
369	P-139	quinaprilat
370	P-139	ramipril
371	P-139	saralasin acetate
372	P-139	spirapril
373	P-139	temocapril
374	P-139	trandolapril
375	P-140	alacepril
376	P-140	benazepril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
377	P-140	captopril
378	P-140	ceronapril
379	P-140	cilazapril
380	P-140	delapril
381	P-140	enalapril
382	P-140	enalaprilat
383	P-140	fosinopril
384	P-140	fosinoprilat
385	P-140	imadapril
386	P-140	lisinopril
387	P-140	moexipril
388	P-140	moveltipril
389	P-140	perindopril
390	P-140	quinapril
391	P-140	quinaprilat
392	P-140	ramipril
393	P-140	saralasin acetate
394	P-140	spirapril
395	P-140	temocapril
396	P-140	trandolapril

[162] **Table 11** illustrates additional examples of some of the combinations of the present invention wherein the combination comprises a first amount of a reported p38-kinase inhibitor and a second amount of an ACE inhibitor:

Table 11

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
397	P-141	alacepril
398	P-141	benazepril
399	P-141	captopril
400	P-141	ceronapril
401	P-141	cilazapril
402	P-141	delapril
403	P-141	enalapril
404	P-141	enalaprilat
405	P-141	fosinopril
406	P-141	fosinoprilat
407	P-141	imadapril
408	P-141	lisinopril
409	P-141	moexipril
410	P-141	moveltipril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
411	P-141	perindopril
412	P-141	quinapril
413	P-141	quinaprilat
414	P-141	ramipril
415	P-141	saralasin acetate
416	P-141	spirapril
417	P-141	temocapril
418	P-141	trandolapril
419	P-142	alacepril
420	P-142	benazepril
421	P-142	captopril
422	P-142	ceronapril
423	P-142	cilazapril
424	P-142	delapril
425	P-142	enalapril
426	P-142	enalaprilat
427	P-142	fosinopril
428	P-142	fosinoprilat
429	P-142	imadapril
430	P-142	lisinopril
431	P-142	moexipril
432	P-142	moveltipril
433	P-142	perindopril
434	P-142	quinapril
435	P-142	quinaprilat
436	P-142	ramipril
437	P-142	saralasin acetate
438	P-142	spirapril
439	P-142	temocapril
440	P-142	trandolapril
441	P-143	alacepril
442	P-143	benazepril
443	P-143	captopril
444	P-143	ceronapril
445	P-143	cilazapril
446	P-143	delapril
447	P-143	enalapril
448	P-143	enalaprilat
449	P-143	fosinopril
450	P-143	fosinoprilat
451	P-143	imadapril
452	P-143	lisinopril
453	P-143	moexipril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
454	P-143	moveltipril
455	P-143	perindopril
456	P-143	quinapril
457	P-143	quinaprilat
458	P-143	ramipril
459	P-143	saralasin acetate
460	P-143	spirapril
461	P-143	temocapril
462	P-143	trandolapril
463	P-144	alacepril
464	P-144	benazepril
465	P-144	captopril
466	P-144	ceronapril
467	P-144	cilazapril
468	P-144	delapril
469	P-144	enalapril
470	P-144	enalaprilat
471	P-144	fosinopril
472	P-144	fosinoprilat
473	P-144	imadapril
474	P-144	lisinopril
475	P-144	moexipril
476	P-144	moveltipril
477	P-144	perindopril
478	P-144	quinapril
479	P-144	quinaprilat
480	P-144	ramipril
481	P-144	saralasin acetate
482	P-144	spirapril
483	P-144	temocapril
484	P-144	trandolapril
485	P-145	alacepril
486	P-145	benazepril
487	P-145	captopril
488	P-145	ceronapril
489	P-145	cilazapril
490	P-145	delapril
491	P-145	enalapril
492	P-145	enalaprilat
493	P-145	fosinopril
494	P-145	fosinoprilat
495	P-145	imadapril
496	P-145	lisinopril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
497	P-145	moexipril
498	P-145	moveltipril
499	P-145	perindopril
500	P-145	quinapril
501	P-145	quinaprilat
502	P-145	ramipril
503	P-145	saralasin acetate
504	P-145	spirapril
505	P-145	temocapril
506	P-145	trandolapril
507	P-146	alacepril
508	P-146	benazepril
509	P-146	captopril
510	P-146	ceronapril
511	P-146	cilazapril
512	P-146	delapril
513	P-146	enalapril
514	P-146	enalaprilat
515	P-146	fosinopril
516	P-146	fosinoprilat
517	P-146	imadapril
518	P-146	lisinopril
519	P-146	moexipril
520	P-146	moveltipril
521	P-146	perindopril
522	P-146	quinapril
523	P-146	quinaprilat
524	P-146	ramipril
525	P-146	saralasin acetate
526	P-146	spirapril
527	P-146	temocapril
528	P-146	trandolapril
529	P-147	alacepril
530	P-147	benazepril
531	P-147	captopril
532	P-147	ceronapril
533	P-147	cilazapril
534	P-147	delapril
535	P-147	enalapril
536	P-147	enalaprilat
537	P-147	fosinopril
538	P-147	fosinoprilat
539	P-147	imadapril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
540	P-147	lisinopril
541	P-147	moexipril
542	P-147	moveltipril
543	P-147	perindopril
544	P-147	quinapril
545	P-147	quinaprilat
546	P-147	ramipril
547	P-147	saralasin acetate
548	P-147	spirapril
549	P-147	temocapril
550	P-147	trandolapril
551	P-148	alacepril
552	P-148	benazepril
553	P-148	captopril
554	P-148	ceronapril
555	P-148	cilazapril
556	P-148	delapril
557	P-148	enalapril
558	P-148	enalaprilat
559	P-148	fosinopril
560	P-148	fosinoprilat
561	P-148	imadapril
562	P-148	lisinopril
563	P-148	moexipril
564	P-148	moveltipril
565	P-148	perindopril
566	P-148	quinapril
567	P-148	quinaprilat
568	P-148	ramipril
569	P-148	saralasin acetate
570	P-148	spirapril
571	P-148	temocapril
572	P-148	trandolapril
573	P-149	alacepril
574	P-149	benazepril
575	P-149	captopril
576	P-149	ceronapril
577	P-149	cilazapril
578	P-149	delapril
579	P-149	enalapril
580	P-149	enalaprilat
581	P-149	fosinopril
582	P-149	fosinoprilat

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
583	P-149	imadapril
584	P-149	lisinopril
585	P-149	moexipril
586	P-149	moveltipril
587	P-149	perindopril
588	P-149	quinapril
589	P-149	quinaprilat
590	P-149	ramipril
591	P-149	saralasin acetate
592	P-149	spirapril
593	P-149	temocapril
594	P-149	trandolapril
595	P-150	alacepril
596	P-150	benazepril
597	P-150	captopril
598	P-150	ceronapril
599	P-150	cilazapril
600	P-150	delapril
601	P-150	enalapril
602	P-150	enalaprilat
603	P-150	fosinopril
604	P-150	fosinoprilat
605	P-150	imadapril
606	P-150	lisinopril
607	P-150	moexipril
608	P-150	moveltipril
609	P-150	perindopril
610	P-150	quinapril
611	P-150	quinaprilat
612	P-150	ramipril
613	P-150	saralasin acetate
614	P-150	spirapril
615	P-150	temocapril
616	P-150	trandolapril
617	P-151	alacepril
618	P-151	benazepril
619	P-151	captopril
620	P-151	ceronapril
621	P-151	cilazapril
622	P-151	delapril
623	P-151	enalapril
624	P-151	enalaprilat
625	P-151	fosinopril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
626	P-151	fosinoprilat
627	P-151	imadapril
628	P-151	lisinopril
629	P-151	moexipril
630	P-151	moveltipril
631	P-151	perindopril
632	P-151	quinapril
633	P-151	quinaprilat
634	P-151	ramipril
635	P-151	saralasin acetate
636	P-151	spirapril
637	P-151	temocapril
638	P-151	trandolapril
639	P-152	alacepril
640	P-152	benazepril
641	P-152	captopril
642	P-152	ceronapril
643	P-152	cilazapril
644	P-152	delapril
645	P-152	enalapril
646	P-152	enalaprilat
647	P-152	fosinopril
648	P-152	fosinoprilat
649	P-152	imadapril
650	P-152	lisinopril
651	P-152	moexipril
652	P-152	moveltipril
653	P-152	perindopril
654	P-152	quinapril
655	P-152	quinaprilat
656	P-152	ramipril
657	P-152	saralasin acetate
658	P-152	spirapril
659	P-152	temocapril
660	P-152	trandolapril
661	P-153	alacepril
662	P-153	benazepril
663	P-153	captopril
664	P-153	ceronapril
665	P-153	cilazapril
666	P-153	delapril
667	P-153	enalapril
668	P-153	enalaprilat

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
669	P-153	fosinopril
670	P-153	fosinoprilat
671	P-153	imadapril
672	P-153	lisinopril
673	P-153	moexipril
674	P-153	moveltipril
675	P-153	perindopril
676	P-153	quinapril
677	P-153	quinaprilat
678	P-153	ramipril
679	P-153	saralasin acetate
680	P-153	spirapril
681	P-153	temocapril
682	P-153	trandolapril
683	P-154	alacepril
684	P-154	benazepril
685	P-154	captopril
686	P-154	ceronapril
687	P-154	cilazapril
688	P-154	delapril
689	P-154	enalapril
690	P-154	enalaprilat
691	P-154	fosinopril
692	P-154	fosinoprilat
693	P-154	imadapril
694	P-154	lisinopril
695	P-154	moexipril
696	P-154	moveltipril
697	P-154	perindopril
698	P-154	quinapril
699	P-154	quinaprilat
700	P-154	ramipril
701	P-154	saralasin acetate
702	P-154	spirapril
703	P-154	temocapril
704	P-154	trandolapril
705	P-155	alacepril
706	P-155	benazepril
707	P-155	captopril
708	P-155	ceronapril
709	P-155	cilazapril
710	P-155	delapril
711	P-155	enalapril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
712	P-155	enalaprilat
713	P-155	fosinopril
714	P-155	fosinoprilat
715	P-155	imadapril
716	P-155	lisinopril
717	P-155	moexipril
718	P-155	moveltipril
719	P-155	perindopril
720	P-155	quinapril
721	P-155	quinaprilat
722	P-155	ramipril
723	P-155	saralasin acetate
724	P-155	spirapril
725	P-155	temocapril
726	P-155	trandolapril
727	P-156	alacepril
728	P-156	benazepril
729	P-156	captopril
730	P-156	ceronapril
731	P-156	cilazapril
732	P-156	delapril
733	P-156	enalapril
734	P-156	enalaprilat
735	P-156	fosinopril
736	P-156	fosinoprilat
737	P-156	imadapril
738	P-156	lisinopril
739	P-156	moexipril
740	P-156	moveltipril
741	P-156	perindopril
742	P-156	quinapril
743	P-156	quinaprilat
744	P-156	ramipril
745	P-156	saralasin acetate
746	P-156	spirapril
747	P-156	temocapril
748	P-156	trandolapril
749	P-157	alacepril
750	P-157	benazepril
751	P-157	captopril
752	P-157	ceronapril
753	P-157	cilazapril
754	P-157	delapril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
755	P-157	enalapril
756	P-157	enalaprilat
757	P-157	fosinopril
758	P-157	fosinoprilat
759	P-157	imadapril
760	P-157	lisinopril
761	P-157	moexipril
762	P-157	moveltipril
763	P-157	perindopril
764	P-157	quinapril
765	P-157	quinaprilat
766	P-157	ramipril
767	P-157	saralasin acetate
768	P-157	spirapril
769	P-157	temocapril
770	P-157	trandolapril
771	P-158	alacepril
772	P-158	benazepril
773	P-158	captopril
774	P-158	ceronapril
775	P-158	cilazapril
776	P-158	delapril
777	P-158	enalapril
778	P-158	enalaprilat
779	P-158	fosinopril
780	P-158	fosinoprilat
781	P-158	imadapril
782	P-158	lisinopril
783	P-158	moexipril
784	P-158	moveltipril
785	P-158	perindopril
786	P-158	quinapril
787	P-158	quinaprilat
788	P-158	ramipril
789	P-158	saralasin acetate
790	P-158	spirapril
791	P-158	temocapril
792	P-158	trandolapril
793	P-159	alacepril
794	P-159	benazepril
795	P-159	captopril
796	P-159	ceronapril
797	P-159	cilazapril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
798	P-159	delapril
799	P-159	enalapril
800	P-159	enalaprilat
801	P-159	fosinopril
802	P-159	fosinoprilat
803	P-159	imadapril
804	P-159	lisinopril
805	P-159	moexipril
806	P-159	moveltipril
807	P-159	perindopril
808	P-159	quinapril
809	P-159	quinaprilat
810	P-159	ramipril
811	P-159	saralasin acetate
812	P-159	spirapril
813	P-159	temocapril
814	P-159	trandolapril
815	P-160	alacepril
816	P-160	benazepril
817	P-160	captopril
818	P-160	ceronapril
819	P-160	cilazapril
820	P-160	delapril
821	P-160	enalapril
822	P-160	enalaprilat
823	P-160	fosinopril
824	P-160	fosinoprilat
825	P-160	imadapril
826	P-160	lisinopril
827	P-160	moexipril
828	P-160	moveltipril
829	P-160	perindopril
830	P-160	quinapril
831	P-160	quinaprilat
832	P-160	ramipril
833	P-160	saralasin acetate
834	P-160	spirapril
835	P-160	temocapril
836	P-160	trandolapril
837	P-161	alacepril
838	P-161	benazepril
839	P-161	captopril
840	P-161	ceronapril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
841	P-161	cilazapril
842	P-161	delapril
843	P-161	enalapril
844	P-161	enalaprilat
845	P-161	fosinopril
846	P-161	fosinoprilat
847	P-161	imadapril
848	P-161	lisinopril
849	P-161	moexipril
850	P-161	moveltipril
851	P-161	perindopril
852	P-161	quinapril
853	P-161	quinaprilat
854	P-161	ramipril
855	P-161	saralasin acetate
856	P-161	spirapril
857	P-161	temocapril
858	P-161	trandolapril
859	P-162	alacepril
860	P-162	benazepril
861	P-162	captopril
862	P-162	ceronapril
863	P-162	cilazapril
864	P-162	delapril
865	P-162	enalapril
866	P-162	enalaprilat
867	P-162	fosinopril
868	P-162	fosinoprilat
869	P-162	imadapril
870	P-162	lisinopril
871	P-162	moexipril
872	P-162	moveltipril
873	P-162	perindopril
874	P-162	quinapril
875	P-162	quinaprilat
876	P-162	ramipril
877	P-162	saralasin acetate
878	P-162	spirapril
879	P-162	temocapril
880	P-162	trandolapril
881	P-163	alacepril
882	P-163	benazepril
883	P-163	captopril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
884	P-163	ceronapril
885	P-163	cilazapril
886	P-163	delapril
887	P-163	enalapril
888	P-163	enalaprilat
889	P-163	fosinopril
890	P-163	fosinoprilat
891	P-163	imadapril
892	P-163	lisinopril
893	P-163	moexipril
894	P-163	moveltipril
895	P-163	perindopril
896	P-163	quinapril
897	P-163	quinaprilat
898	P-163	ramipril
899	P-163	saralasin acetate
900	P-163	spirapril
901	P-163	temocapril
902	P-163	trandolapril
903	P-164	alacepril
904	P-164	benazepril
905	P-164	captopril
906	P-164	ceronapril
907	P-164	cilazapril
908	P-164	delapril
909	P-164	enalapril
910	P-164	enalaprilat
911	P-164	fosinopril
912	P-164	fosinoprilat
913	P-164	imadapril
914	P-164	lisinopril
915	P-164	moexipril
916	P-164	moveltipril
917	P-164	perindopril
918	P-164	quinapril
919	P-164	quinaprilat
920	P-164	ramipril
921	P-164	saralasin acetate
922	P-164	spirapril
923	P-164	temocapril
924	P-164	trandolapril
925	P-165	alacepril
926	P-165	benazepril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
927	P-165	captopril
928	P-165	ceronapril
929	P-165	cilazapril
930	P-165	delapril
931	P-165	enalapril
932	P-165	enalaprilat
933	P-165	fosinopril
934	P-165	fosinoprilat
935	P-165	imadapril
936	P-165	lisinopril
937	P-165	moexipril
938	P-165	moveltipril
939	P-165	perindopril
940	P-165	quinapril
941	P-165	quinaprilat
942	P-165	ramipril
943	P-165	saralasin acetate
944	P-165	spirapril
945	P-165	temocapril
946	P-165	trandolapril
947	P-166	alacepril
948	P-166	benazepril
949	P-166	captopril
950	P-166	ceronapril
951	P-166	cilazapril
952	P-166	delapril
953	P-166	enalapril
954	P-166	enalaprilat
955	P-166	fosinopril
956	P-166	fosinoprilat
957	P-166	imadapril
958	P-166	lisinopril
959	P-166	moexipril
960	P-166	moveltipril
961	P-166	perindopril
962	P-166	quinapril
963	P-166	quinaprilat
964	P-166	ramipril
965	P-166	saralasin acetate
966	P-166	spirapril
967	P-166	temocapril
968	P-166	trandolapril
969	P-167	alacepril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
970	P-167	benazepril
971	P-167	captopril
972	P-167	ceronapril
973	P-167	cilazapril
974	P-167	delapril
975	P-167	enalapril
976	P-167	enalaprilat
977	P-167	fosinopril
978	P-167	fosinoprilat
979	P-167	imadapril
980	P-167	lisinopril
981	P-167	moexipril
982	P-167	moveltipril
983	P-167	perindopril
984	P-167	quinapril
985	P-167	quinaprilat
986	P-167	ramipril
987	P-167	saralasin acetate
988	P-167	spirapril
989	P-167	temocapril
990	P-167	trandolapril
991	P-168	alacepril
992	P-168	benazepril
993	P-168	captopril
994	P-168	ceronapril
995	P-168	cilazapril
996	P-168	delapril
997	P-168	enalapril
998	P-168	enalaprilat
999	P-168	fosinopril
1000	P-168	fosinoprilat
1001	P-168	imadapril
1002	P-168	lisinopril
1003	P-168	moexipril
1004	P-168	moveltipril
1005	P-168	perindopril
1006	P-168	quinapril
1007	P-168	quinaprilat
1008	P-168	ramipril
1009	P-168	saralasin acetate
1010	P-168	spirapril
1011	P-168	temocapril
1012	P-168	trandolapril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
1013	P-169	alacepril
1014	P-169	benazepril
1015	P-169	captopril
1016	P-169	ceronapril
1017	P-169	cilazapril
1018	P-169	delapril
1019	P-169	enalapril
1020	P-169	enalaprilat
1021	P-169	fosinopril
1022	P-169	fosinoprilat
1023	P-169	imadapril
1024	P-169	lisinopril
1025	P-169	moexipril
1026	P-169	moveltipril
1027	P-169	perindopril
1028	P-169	quinapril
1029	P-169	quinaprilat
1030	P-169	ramipril
1031	P-169	saralasin acetate
1032	P-169	spirapril
1033	P-169	temocapril
1034	P-169	trandolapril
1035	P-170	alacepril
1036	P-170	benazepril
1037	P-170	captopril
1038	P-170	ceronapril
1039	P-170	cilazapril
1040	P-170	delapril
1041	P-170	enalapril
1042	P-170	enalaprilat
1043	P-170	fosinopril
1044	P-170	fosinoprilat
1045	P-170	imadapril
1046	P-170	lisinopril
1047	P-170	moexipril
1048	P-170	moveltipril
1049	P-170	perindopril
1050	P-170	quinapril
1051	P-170	quinaprilat
1052	P-170	ramipril
1053	P-170	saralasin acetate
1054	P-170	spirapril
1055	P-170	temocapril

Example Combination No.	p38-kinase inhibitor	ACE inhibitor
1056	P-170	trandolapril

[163] It should be recognized that the above tables simply illustrate examples of various combinations of p38-kinase inhibitors with various ACE inhibitors. This invention therefore should not be limited to those combinations.

[164] It should also be recognized that this invention contemplates combinations comprising more than one p38-kinase inhibitor with an ACE inhibitor, as well as combinations comprising a p38-kinase inhibitor with more than one ACE inhibitor, as well as combinations comprising more than one p38-kinase inhibitor with more than one ACE inhibitor. Further, any such combination (or any combination comprising only one p38-kinase inhibitor and only one ACE inhibitor) may further comprise one or more aldosterone antagonists, one or more diuretics, and/or one or more other therapeutic agents. Such other therapeutic agents may include, for example, one or more inhibitors of ileal bile transporter activity ("IBAT inhibitors"), inhibitors of cholesterol ester transfer protein activity ("CETP inhibitors"), fibrates, digoxin, calcium channel blockers, endothelin antagonists, inhibitors of microsomal triglyceride transfer protein, cholesterol absorption antagonists, phytosterols, bile acid sequestrants, vasodilators, adrenergic blockers, adrenergic stimulants, and/or inhibitors of HMG-CoA reductase activity. Such other therapeutic agents may also comprise, for example, one or more conventional anti-inflammatories, such as steroids, cyclooxygenase-2 inhibitors, disease-modifying anti-rheumatic drugs ("DMARDs"), immunosuppressive agents, non-steroidal anti-inflammatory drugs ("NSAIDs"), 5-lipoxygenase inhibitors, LTB4 antagonists, and LTA4 hydrolase inhibitors.

F. Preferred Modes of Administration

[165] The therapeutic agents used in this invention may be administered by any means that produces contact of each agent with its site of action in the body. Each therapeutic agent may each be administered as, for example, a compound *per se* or a pharmaceutically-acceptable salt thereof. Pharmaceutically-acceptable salts are often particularly suitable for medical applications because of their greater aqueous solubility

relative to the compounds themselves. Typically, all the therapeutic agents are preferably administered orally. This invention, however, also contemplates methods wherein at least one of the therapeutic agents is administered by another means, such as parenterally.

[166] In many embodiments, a therapeutic agent used in this invention is administered as part of a pharmaceutical composition (or medicament) that further comprises one or more pharmaceutically-acceptable carriers, diluents, wetting or suspending agents, vehicles, and/or adjuvants (the carriers, diluents, wetting or suspending agents, vehicles, and adjuvants sometimes being collectively referred to in this specification as "carrier materials"); and/or other active ingredients. Where the agent is administered as part of a combination therapy, the other agent(s) of the combination may also be contained in the same pharmaceutical composition or as a part of a separate pharmaceutical composition or both.

[167] In many preferred embodiments, the pharmaceutical composition is in the form of a dosage unit containing a particular amount of the active ingredient(s). For example, a pharmaceutical composition comprising a p38-kinase inhibitor preferably comprises a dosage form containing from about 0.1 to 1000 mg of the p38-kinase inhibitor, and more typically from about 7.0 to about 350 mg of the p38-kinase inhibitor. Illustrating further, many ACE inhibitors are commercially available in pre-set dosage forms. For example, captopril is sold by E.R. Squibb & Sons, Inc. (Princeton, N.J.) (now part of Bristol-Myers-Squibb) under the trademark "CAPOTEN" in tablet dosage form at doses of 12.5, 50, and 100 mg per tablet. Enalapril is sold by Merck & Co (West Point, PA) under the trademark "VASOTEC" in tablet dosage form at doses of 2.5 mg, 5 mg, 10 mg, and 20 mg per tablet. And Lisinopril is sold by Merck & Co under the trademark "PRINIVIL" in tablet dosage form at doses of 5, 10, 20, and 40 mg per tablet.

[168] In many embodiments, from about 0.05 to about 95% by weight of a pharmaceutical composition consists of an active therapeutic agent(s). The preferred composition depends on the method of administration. Pharmaceutical compositions suitable for this invention may be prepared by a variety of well-known techniques of pharmacy that include the step of bringing into association the therapeutic agent(s) with the carrier material(s). In general, the compositions are prepared by uniformly and intimately admixing the therapeutic agent(s) with a liquid or finely divided solid carrier material (or both), and then, if desirable, shaping the product. For example, a tablet may